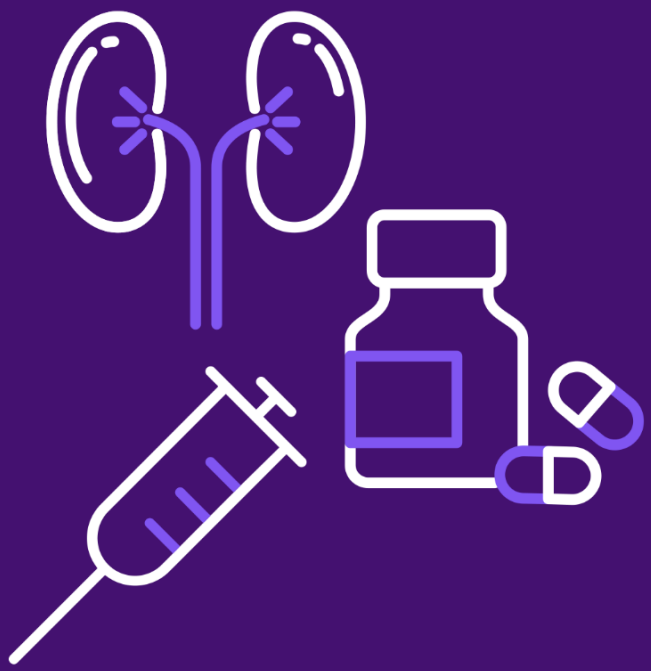
NSW GOVERNMENT

International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)

2022



eviQ

We acknowledge the Traditional Custodians of the lands and seas on which we work and live, and pay our respects to Elders, past, present and future.

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Guideline disclaimer

The ADDIKD guideline was developed by an expert clinician and academic volunteer working group using the GRADE approach of analysing available scientific and clinical evidence and accepted approaches in nephrology, clinical pharmacology, and cancer care. The guideline is targeted at clinicians. Patients, or other community members using these guidelines should do so in conjunction with a health professional. With the emergence of new evidence from the time of guideline development and publication, its content may not be considered as inclusive of all treatments or models of care. ADDIKD is not intended to be prescriptive, but to guide clinical decision-making where anticancer drugs will be used in patients with chronic kidney dysfunction. Patient care and treatment should always be based on the individual patient's specific clinical circumstances and independent professional judgement of the treating clinical team. Cancer Institute NSW and eviQ assume no responsibility for any injury or damage to persons or property related to use of this information or any errors or omissions.

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ADDIKD is endorsed by:

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Foreword

Australia's National Medicines Policy articulates the importance of access to and appropriate use of medicines. Implicit in this framework is the expectation that health professionals will prescribe medicines in a safe and effective manner. Prescribing anti-cancer treatments is inherently complex, and this is even more so for patients with renal or hepatic dysfunction. Renal dysfunction is common in cancer patients because of comorbidities, acute illness, the direct effects of the tumour or the toxicity of chemotherapy. There is a pressing need for guidance on how to assess kidney function in individuals with cancer, and how to adjust dosing in the setting of renal dysfunction. However, addressing this need presents many challenges. Over the past decade, eviQ has attempted to tackle this difficult issue on at least three separate occasions. This document draws on the lessons of past attempts, as well as our latest concerted effort, and now culminates in this first International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

To develop ADDIKD, eviQ incorporated the highest level of evidence assessment, combined with the practical aspects of delivering cancer treatment. We started this process by drawing on the internationally recognised expertise of our colleagues in renal medicine and were able to achieve consensus on the assessment of kidney function using eGFR (estimated glomerular filtration rate). This was a significant step forward in cancer care and paved the way for harmonising assessments across all medical specialities, general practitioners, and pharmacists. Having established eGFR as the gold standard for assessing renal dysfunction, we then moved to establish and apply a tailored and consistent approach to dosing adjustment for individual drugs.

The development of ADDIKD would not have been achieved without the time and effort of dedicated members of the ADDIKD Working Group, as well as invited experts from nephrology, clinical pharmacology, cancer care, clinical pathology, geriatrics, and methodologists from around the globe.

We trust that this guideline will be internationally recognised as an evidence-based resource for improving prescribing of anticancer medications. We hope that it will not only be adopted by clinicians but used as an educational tool and incorporated into future clinical trials and research studies.

For eviQ, this is a further step on our 20-year commitment to improving cancer outcomes.

Professor Robyn Ward

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and Chair of ADDIKD Working Group

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Acknowledgements

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Contents

Summary of key recommendations

Where an action is "*recommended*", the strength of the statement is strong and most patients should receive the recommended course of action. Where an action is "*suggested*", the strength of the statement is conditional as different choices will be appropriate for different patients (see *Methods).*

Kidney function assessment in adult cancer patients

1. **We recommend the use of estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$) equation to guide the assessment of kidney function, except where directly measured glomerular filtration rate (mGFR) is clinically necessary**.

1.1. Directly mGFR remains the most accurate method of assessing kidney function in cancer patients but can be difficult to access routinely and is costly.

1.2. $eGFR_{CKD\text{-}EPI}$ is a more accurate and precise estimation of directly mGFR than other estimation methods of kidney function. $eGFR_{CKD\text{-}EPI}$ is reported automatically in pathology results, accounts for creatinine assay standardisation, and aligns with international nephrology recommendations.

1.3. $eGFR_{CKD\text{-}EPI}$ requires stable kidney function and should be performed as close as possible to the time of administering the anticancer drug(s) to ensure it is a reflective estimation of the patient's steady state kidney function. This is especially important if the anticancer drug(s) is guided by kidney function for dosing and/or demonstrates nephrotoxic potential, where $eGFR_{CKD\text{-}EPI}$ < 60 mL/min/1.73 m^2, where the patient is acutely unwell (or has recently recovered from an acute illness) or displays signs of unstable kidney function (including development of acute kidney injury).

1.4. $eGFR_{CKD\text{-}EPI}$ may be unreliable in certain clinical situations involving, but not limited to, extremes of body size or muscle mass (e.g., obesity, non-obese sarcopenia, high muscle mass), amputees, persons with paraplegia or conditions of skeletal muscle, individuals with exceptional dietary habits (e.g., creatine supplements), advanced liver disease, untreated hypothyroidism, drugs interfering with creatinine secretion or the creatinine assay, and ureteric obstruction.

1.5. $eGFR_{CKD\text{-}EPI}$ is unsuitable for assessing kidney function in kidney replacement therapy, pregnant women, and patients < 18 years of age.

Application of kidney function assessment to guide dosing of anticancer drugs

The guideline does *not* include the dosing of anticancer drugs (see *Scope of guideline* for details):

- beyond the first cycle of treatment
- in acute kidney injury or unstable kidney function
- in stem cell mobilisation, bone marrow transplantation and cellular therapies
- in patients < 18 years of age
- in pregnant women
- in various types of kidney replacement therapy

2. We recommend $eGFR_{CKD\text{-}EPI}$ to guide the dosing of anticancer drugs whose dose is dependent on kidney function, except in specific clinical situations or for a select group of anticancer drugs where $eGFR_{CKD\text{-}EPI}$ may be unsuitable.

2.1 Directly mGFR is preferred to guide the initial dosing for a select group of anticancer drugs including, but not limited to, carboplatin, cisplatin, and methotrexate (≥ 500 mg/m^2).

Directly mGFR is preferred to guide the initial dosing of anticancer drugs whose dose is dependent on kidney function in specific clinical situations involving, but not limited to, patients with extremes of body size or muscle mass, amputees, persons with paraplegia or conditions of skeletal muscle.

2.2 $eGFR_{CKD\text{-}EPI}$ adjusted to an individual's body surface area (BSA) is not routinely advised to guide dosing of anticancer drugs over standardised $eGFR_{CKD\text{-}EPI}$ within ADDIKD, except for carboplatin. Anticancer drug dosing based on weight descriptors (e.g., BSA, weight) may impact the performance of BSA-adjusted $eGFR_{CKD\text{-}EPI}$ to guide dosing, especially, as body size/composition will be accounted for twice in dose calculation.

2.3 BSA-adjusted $eGFR_{CKD\text{-}EPI}$ is a suitable alternative to directly mGFR for use in the Calvert formula when dosing carboplatin, especially where eGFR 45 – 125 mL/min/1.73 m^2, treatment intent is non-curative and the patient is neither an amputee, paraplegic or has conditions of skeletal muscle and is without extremes of body size or muscle mass. Directly mGFR is the preferred kidney function value in other clinical situations.

2.4 When dosing anticancer drugs in the presence of kidney dysfunction, carefully consider:

- Patient factors – clinical condition (e.g., hydration status, performance status), comorbidities (e.g., liver dysfunction), genetic polymorphisms (if applicable), factors influencing kidney function (e.g., presence of a single or horseshoe kidney, kidney transplant,

dialysis) and attitude/beliefs towards treatment.

- Treatment factors – treatment protocol (e.g., intent of treatment, appropriate alternative treatment protocols with similar efficacy and without drugs dependent on kidney function for dosing), risk of adverse events (e.g., tumour lysis syndrome), anticancer drug properties (e.g., pharmacokinetics, pharmacodynamics, formulation, availability of therapeutic drug monitoring), and concomitant drugs (especially with nephrotoxic potential).
- Other – accessibility to directly mGFR, and the evidence and strength behind dose recommendations.

3. We recommend the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD) categories to guide the stepwise dose adjustment of anticancer drugs in kidney dysfunction and the monitoring of drug-related adverse events.

Anticancer drugs and their dosing in kidney dysfunction

4.1 The use of kidney function to inform the initial dosing is:

- **recommended** for bleomycin, capecitabine, carboplatin, cisplatin, cyclophosphamide, etoposide (including etoposide *phosphate*), fludarabine, lenalidomide, methotrexate, raltitrexed, and topotecan.
- **suggested** for high-dose cytarabine (≥ 1000 mg/m^2), dacarbazine, daunorubicin (including *liposomal* daunorubicin), fluorouracil, idarubicin, ifosfamide, irinotecan, melphalan, mercaptopurine, mitomycin, oxaliplatin, pemetrexed, procarbazine and vinflunine.
- **recommended *against***, **but kidney function may inform the monitoring of adverse events and the selection of an alternative treatment protocol**, for obinutuzumab, and venetoclax.
- **recommended *against***, **but kidney function may inform the**

monitoring of adverse events, for bendamustine, cabazitaxel, chlorambucil, gemcitabine, paclitaxel, and thalidomide.

- **suggested *against*, but kidney function may inform the monitoring of adverse events**, for azacitidine, bevacizumab, bortezomib, dactinomycin, *pegylated liposomal* doxorubicin, everolimus, nab-paclitaxel, temozolomide, and thiotepa.
- **recommended *against*** for cetuximab, dabrafenib, docetaxel, doxorubicin, epirubicin, nivolumab, panitumumab, pembrolizumab, vinblastine, vincristine, vindesine, and vinorelbine.
- **suggested *against*** for low-dose cytarabine (< 1000 mg/m^2), durvalumab, pertuzumab, rituximab, trastuzumab, and trastuzumab emtansine.

4.2 The use of KDIGO CKD categories in kidney dysfunction is:

- **suggested to guide the dose adjustment and the monitoring for drug-related adverse events** for bleomycin, capecitabine, cisplatin, cyclophosphamide, high-dose cytarabine (≥ 1000 mg/m^2), dacarbazine, daunorubicin (including *liposomal* daunorubicin), etoposide (including etoposide *phosphate*), fludarabine, fluorouracil, idarubicin, ifosfamide, irinotecan, lenalidomide, melphalan, mercaptopurine, methotrexate, mitomycin, methotrexate, oxaliplatin, pemetrexed, procarbazine, raltitrexed, topotecan, and vinflunine.
- **recommended *against* to guide the dose adjustment** for carboplatin.
- **suggested to guide monitoring for drug-related adverse events** for azacitidine, bendamustine, bortezomib, carboplatin, dactinomycin, *pegylated liposomal* doxorubicin, gemcitabine, nab-paclitaxel, and temozolomide.

4.3 An initial dose reduction or a clinically appropriate alternative treatment protocol, under specific conditions, is:

- **recommended for**
  - **eGFR < 60 mL/min/1.73 m^2** in capecitabine, cisplatin, fludarabine, lenalidomide, methotrexate, raltitrexed, and topotecan.
  - **eGFR < 45 mL/min/1.73 m^2** in bleomycin and etoposide (including etoposide *phosphate*).
- **suggested for**
  - **eGFR < 60 mL/min/1.73 m^2** in high-dose cytarabine (≥ 1000 mg/m^2), fluorouracil, melphalan, mercaptopurine, and vinflunine.
  - **eGFR < 45 mL/min/1.73 m^2** in ifosfamide, pemetrexed, and procarbazine.
  - **eGFR < 30 mL/min/1.73 m^2** in cyclophosphamide, dacarbazine, daunorubicin (including *liposomal* daunorubicin), idarubicin, irinotecan, mitomycin, and oxaliplatin.
- **suggested *against* for < 60 mL/min/1.73 m^2** azacitidine, bendamustine, bortezomib, low-dose cytarabine (< 1000 mg/m^2), dactinomycin, *pegylated liposomal doxorubicin*, gemcitabine, nab-paclitaxel, and temozolomide.
- **suggested *against* for eGFR < 60 mL/min/1.73 m^2** in carboplatin, but use the **Calvert formula with a target area under the curve** for dosing instead.

See *Table 1* for summary of initial dosing recommendations in kidney dysfunction for all drugs in ADDIKD.

Table 1 – Summary of initial dose recommendations of anticancer drugs in kidney dysfunction

ANTICANCER DRUG DOSE RECOMMENDATIONS IN KIDNEY DYSFUNCTION		
eGFR (mL/min/1.73 m²)	**Dose** [a]	**Drugs**
45 – 59	**full dose**	Recommended for • cabazitaxel, cetuximab, chlorambucil, dabrafenib, docetaxel, doxorubicin, epirubicin, nivolumab, paclitaxel, panitumumab, pembrolizumab, thalidomide, vinblastine, vincristine, vindesine, vinorelbine. Suggested for • azacitidine, bendamustine, bortezomib, cyclophosphamide, low-dose cytarabine (< 1000 mg/m²), dacarbazine, *pegylated liposomal* doxorubicin, durvalumab, idarubicin, oxaliplatin, nab-paclitaxel, pertuzumab, procarbazine, rituximab, temozolomide, trastuzumab, trastuzumab emtansine.
	full dose	Recommended, but kidney function may inform the monitoring of adverse events for • bleomycin, etoposide (including etoposide *phosphate*), obinutuzumab, venetoclax. Suggested, but kidney function may inform the monitoring of adverse events for • bevacizumab, dactinomycin, daunorubicin (including *liposomal* daunorubicin), everolimus, gemcitabine, ifosfamide, irinotecan, mitomycin, pemetrexed, thiotepa.
	dose reduction and/or alternative protocol	Recommended for • capecitabine, cisplatin, fludarabine, lenalidomide, methotrexate, raltitrexed, topotecan. Suggested for • high-dose cytarabine (≥ 1000 mg/m²), fluorouracil, melphalan, mercaptopurine, vinflunine.
	target AUC using Calvert formula	Suggested, but kidney function may inform the monitoring of adverse events for • carboplatin.
30 – 44	**full dose**	Recommended for • cabazitaxel, cetuximab, dabrafenib, docetaxel, doxorubicin, epirubicin, nivolumab, paclitaxel, panitumumab, pembrolizumab, thalidomide, vinblastine, vincristine, vindesine, vinorelbine. Suggested for • azacitidine, bendamustine, bortezomib, cyclophosphamide, low-dose cytarabine (< 1000 mg/m²), dacarbazine, *pegylated liposomal* doxorubicin, durvalumab, idarubicin, oxaliplatin, nab-paclitaxel, pertuzumab, rituximab, temozolomide, trastuzumab, trastuzumab emtansine.
	full dose	Recommended, but kidney function may inform the monitoring of adverse events for • chlorambucil, obinutuzumab, venetoclax. Suggested, but kidney function may inform the monitoring of adverse events for • bevacizumab, dactinomycin, daunorubicin (including *liposomal* daunorubicin), everolimus, gemcitabine, irinotecan, mitomycin, thiotepa.
	dose reduction and/or alternative protocol	Recommended for • bleomycin, capecitabine, etoposide (including etoposide *phosphate*), fludarabine, lenalidomide, methotrexate, raltitrexed, topotecan. Suggested for • high-dose cytarabine (≥ 1000 mg/m²), fluorouracil, ifosfamide, melphalan, mercaptopurine, pemetrexed, procarbazine vinflunine.
	target AUC using Calvert formula	Suggested, but kidney function may inform the monitoring of adverse events for • carboplatin.
	AVOID	Recommended for • cisplatin.
15 – 29	**full dose**	Recommended for • cabazitaxel, cetuximab, dabrafenib, docetaxel, doxorubicin, epirubicin, nivolumab, paclitaxel, panitumumab, pembrolizumab, vinblastine, vincristine, vindesine, vinorelbine. Suggested for • low-dose cytarabine (< 1000 mg/m²), durvalumab, pertuzumab, rituximab, trastuzumab, trastuzumab emtansine.
	full dose	Recommended, but kidney function may inform the monitoring of adverse events for • chlorambucil, thalidomide. Suggested, but kidney function may inform the monitoring of adverse events for • azacitidine, bendamustine, bevacizumab, bortezomib, dactinomycin, *pegylated liposomal* doxorubicin, everolimus, gemcitabine, nab-paclitaxel, temozolomide, thiotepa.
	dose reduction and/or alternative protocol	Recommended for • bleomycin, etoposide (including etoposide *phosphate*), lenalidomide, obinutuzumab, venetoclax. Suggested for • cyclophosphamide, dacarbazine, daunorubicin (including *liposomal* daunorubicin), fluorouracil, idarubicin, ifosfamide, irinotecan, melphalan, mercaptopurine, oxaliplatin, procarbazine, vinflunine.
	target AUC using Calvert formula	Suggested, but kidney function may inform the monitoring of adverse events for • carboplatin.
	AVOID	Recommended for • capecitabine, cisplatin, fludarabine, methotrexate, raltitrexed, topotecan. Suggested for • high-dose cytarabine (≥ 1000 mg/m²), mitomycin, pemetrexed.
< 15 (without KRT)	**full dose**	Recommended for • cetuximab, docetaxel, doxorubicin, nivolumab, panitumumab, pembrolizumab, vinblastine, vincristine, vindesine, vinorelbine. Suggested, for • low-dose cytarabine (< 1000 mg/m²), durvalumab, pertuzumab, rituximab, trastuzumab, trastuzumab emtansine.
	full dose	Recommended, but kidney function may inform the monitoring of adverse events for • cabazitaxel, paclitaxel, thalidomide. Suggested, but kidney function may inform the monitoring of adverse events for • bendamustine, bevacizumab, bortezomib.
	dose reduction and/or alternative protocol	Recommended for • lenalidomide, venetoclax.
	AVOID	Recommended for • bleomycin, capecitabine, cisplatin, fludarabine, methotrexate, raltitrexed, topotecan. Suggested for • high-dose cytarabine (≥ 1000 mg/m²), mitomycin, pemetrexed.
	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	Recommend for • chlorambucil, dabrafenib, epirubicin, etoposide (including etoposide *phosphate*), obinutuzumab. Suggested for • azacitidine, carboplatin, cyclophosphamide, dacarbazine, dactinomycin, daunorubicin (including *liposomal* daunorubicin), *pegylated liposomal* doxorubicin, everolimus, fluorouracil, gemcitabine, idarubicin, ifosfamide, irinotecan, melphalan, mercaptopurine, oxaliplatin, nab-paclitaxel, procarbazine, temozolomide, thiotepa, vinflunine.
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

[a] Proposed dosing under specific circumstances (see ADDIKD's *Drug specific recommendations* for individual drug details)

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

Background

Safe and effective treatment with anticancer drugs is complicated by factors such as a narrow therapeutic index, large intra-individual and inter-individual pharmacokinetic variability, and the need to use multi-drug, multi-day chemotherapy protocols. Kidney function is a common dosing consideration in cancer patients to ensure tolerable, yet effective, anticancer drug treatment, as this organ is a primary site of drug clearance (CL) and elimination for many drugs.

Kidney dysfunction reportedly occurs in 12 – 25% of cancer patients at treatment initiation,[1-13] although prevalence is higher in some patient populations such as those with cancer of the lung, colorectal, prostate or multiple myeloma.[4,14] However, patients with chronic kidney disease (CKD), especially recipients of kidney replacement therapy ([KRT], receiving dialysis or a kidney transplant) are at higher risk of malignancies than the general population.[2,15,16] As the incidence of cancer increases with the ageing population (global rates are expected to double in people aged ≥ 65 years over the next 20 years, representing 60% of the worldwide cancer incidence),[17] the physiological changes to the kidney associated with ageing become more significant in the context of drug CL and elimination. Glomerular filtration rates (GFR) drop by an estimated 1 mL/min per year after 40 years of age.[18] Studies have found an association between kidney dysfunction (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) and cancer-related mortality, where individuals with normal kidney function (eGFR ≥ 60 mL/min/1.73 m^2) survive on average, 8.6 months longer than those with compromised kidney function.[1,12,13] Studies suggest rates of cancer-related mortality may increase up to 25 – 29% in kidney dysfunction (> 2.5-fold higher in KRT than the general population),[2,19] with an 18% increased risk of death from cancer with every 10 mL/min/1.73 m^2 decline in eGFR < 60 mL/min/1.73 m^2.[1]

In clinical practice, numerous methods to assess kidney function are used in cancer patients, from estimation formulas to direct measurements of GFR. The gold standard for precise kidney function assessment is the direct measurement of the clearance of exogenous markers (freely filtered by the glomerulus and neither reabsorbed or secreted by the tubules) such as iohexol, iothalamate, ^{51}Cr-EDTA (radioactive chromium complex with ethylene diamine tetracetic acid) or ^{99m}Tc-DTPA (TC-diethylenetriaminepentaacetic acid), referred to as directly measured glomerular filtration rate (mGFR).[20] However, procuring a directly mGFR may be costly, more time-consuming and may not be readily accessible in comparison to other assessment methods.

The estimation of kidney function in clinical practice often involves equations that use a more accessible biochemical marker, serum creatinine (S_{Cr}); the breakdown product of skeletal muscle that is freely filtered by the glomerulus and actively secreted (20 – 30%) through the proximal tubule.[21] Creatinine clearance (CrCl), determined using the Cockcroft-Gault equation, is frequently used as a surrogate indicator of GFR.[22,23] Despite being convenient and widely utilised in drug dosing, the Cockcroft-Gault equation, developed in the 1970s using measured CrCl from 24-hour urine collections, has a perceived accuracy which has not been confirmed following the use of the isotope dilution mass spectrometry standardisation of S_{Cr} assay in 2010.[22-24] Furthermore, CrCl overestimates actual GFR (a direct indicator of kidney function) by 10 – 20% as it includes creatinine filtered through the glomerulus and via tubular secretion.[21] Newer GFR estimation methods accounting for the S_{Cr} assay standardisation and developed using iothalamate GFR measurement (directly mGFR), include the Modification of Diet in Renal Disease (MDRD)[25] and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)[26] formulas.

Kidney Disease: Improving Global Outcomes (KDIGO), an international network providing gold standard and evidence-based guidelines in nephrology, recommended in the 2012 Chronic Kidney Disease Guideline[27] clinicians use eGFR in the initial assessment of kidney function, and that laboratories report eGFR using the CKD-EPI equation. Their threshold for decreased kidney function is eGFR < 60 mL/min/1.73 m^2 (half the normal eGFR for young adults), with further GFR categories describing the severity of decline in kidney function. These standardised practice recommendations in kidney disease are seldom reflected in drug dosing references where considerable variations exist in assessing and defining levels of kidney function to guide dose adjustment.[28-31]

Kidney dysfunction may alter the pharmacokinetics of drugs primarily eliminated through the kidneys by decreasing CL, prolonging the half-life ($t_{½}$) of parent drug/active metabolites and/or altering the volume of distribution (V_d) (e.g., hypoalbuminaemia causing an increased unbound fraction of certain drugs which are highly protein bound).[14,32] Consequently, higher systemic drug exposure (area under the curve [AUC], maximum concentration [C_{max}]) potentially causes unwanted toxicity, delaying further treatment and compromising dose intensity. Certain anticancer drugs may compound pre-existing kidney dysfunction due to their nephrotoxic potential.

Despite kidney dysfunction posing an important dosing dilemma in clinical practice, current recommendations are largely empirical, based on sparse data and derived from case reports or small cohort studies.[33] Clinical trials further confound this issue by basing their drug dose adjustments on outdated or theoretical data and by excluding patients with kidney dysfunction from studies.[33] Inconsistencies with criteria to define severity of kidney dysfunction, absence of a standardised method of assessing kidney function and the magnitude of dose reductions for the same drug between different treatment protocols with similar treatment intent, highlight the possibility of unnecessary underdosing or overdosing.[33]

The ***International Consensus Guideline on Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)*** has been developed in accordance with international best practice using a framework that aligns with the 2016 National Health and Medical Research Council Standards for Guidelines.[34,35] *ADDIKD* provides a **standardised approach** to anticancer drug dosing in kidney dysfunction, founded on **evidence-based literature** and formulated by an expert clinical working group, addressing the paucity in data by providing **consensus recommendations**.

Scope of guideline

ADDIKD aims to be a **supportive decision-making tool** which prompts clinicians to consider the specific risks and benefits of anticancer drug dose adjustments in kidney dysfunction. This document uses **current evidence** and **expert clinical consensus** to guide **anticancer drug dosing** and **monitoring** of adverse events in this complex patient population.

The guideline includes:

- A standardised approach to **quantifying kidney function** in the adult cancer patient.
- A standardised **classification** of kidney dysfunction to aid consistency in applying dose adjustment to anticancer drugs across clinical settings.
- Anticancer drug **dosing recommendations** for the ***first cycle of treatment*** using standardised categories of kidney dysfunction, developed through critical review of available evidence and consensus decisions.
- Easy-to-use recommendations for the multidisciplinary cancer team, including members who are less familiar with anticancer drugs or treatment protocols.

The guideline does ***not*** address and does ***not*** apply to, the following situations:

- Dose adjustment in kidney dysfunction beyond the first cycle of treatment (an assessment of the patient's tolerance to the dose used in the first cycle is required before determining doses for subsequent cycles).
- Dosing in acute kidney injury (AKI) or unstable kidney function.
- Dose adjustment for kidney dysfunction in stem cell mobilisation, bone marrow transplantation and cellular therapies. In these circumstances, the transplant team should be consulted if the patient has kidney dysfunction and is requiring one of these drugs referred to in *ADDIKD* as part of their treatment.
- Specific dosing instructions in kidney failure (eGFR < 15 mL/min/1.73 m^2 with or without KRT. The guideline will explicitly highlight in the dosing recommendation whether an anticancer drug should be avoided or alternatively continued at full dose in eGFR < 15 mL/min/1.73 m^2 without KRT. For all other instances in eGFR < 15 mL/min/1.73 m^2 or in KRT, consultation with a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing is advised.
- Dosing in patients < 18 years of age with kidney dysfunction.
- Dosing in pregnant women with kidney dysfunction.

Methods

Following internationally accepted guideline methodology frameworks, an expert international multidisciplinary working group (*ADDIKD Content Development Working Group*) was established which included oncologists, haematologists, nephrologists, clinical pharmacologists, cancer pharmacists, nephrology pharmacists and guideline development experts.

Part 1 – General ADDIKD recommendations

Based on KDIGO recommendations and critical appraisal of the literature, the *Content Development Working Group,* along with additional selected experts in nephrology, pharmacometrics, geriatrics, clinical pharmacology, and clinical pathology, drafted recommendations for:

1. a standardised approach to assessing kidney function in cancer patients
2. the application of this standardised approach to anticancer drug dosing
3. using KDIGO's CKD categories to guide anticancer drug dosing and monitoring in kidney dysfunction.

A virtual workshop was conducted, inviting key external stakeholders in cancer care, nephrology, clinical pharmacology, academia, representatives from government, pharmaceutical industry, and consumers, with the objective of attaining wider agreement on these recommendations. Anonymous voting was conducted on the recommendations to achieve consensus.

These recommendations underpin the consistency of the *ADDIKD* guideline and its progression to Part 2.

Part 2 – Drug-specific ADDIKD recommendations

An initial working group meeting in August 2018 prioritised the key clinical questions and the drugs to be addressed in Part 2. The three questions were formulated according to the PI/ECO (Patient/Problem, Intervention/Exposure, Comparison or Control, Outcome) approach[36] (see *Appendix 1 – Key clinical questions*):

1. *Should renal elimination versus non-renal elimination be used to direct dosing of this anticancer drug?*
2. *Should full dose versus reduced dose of this anticancer drug be used in patients with kidney dysfunction?*
3. *Should the KDIGO CKD categories be used in the dose adjustment of this anticancer drug in kidney dysfunction?*

The key clinical questions provided the strategy for an extensive primary evidence literature search (PubMed, Cochrane Library and EMBASE databases), along with a grey literature search and investigation of registered drug production information for specific anticancer drugs. Identified records were screened and assessed for eligibility by two independent reviewers (see *Appendix 2 – Literature search strategy* for inclusion criteria and search strategy details).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to critically appraise the quality and strength of evidence from the identified records.[34,37] Evidence profiles for each anticancer drug per clinical question were constructed assessing the certainty of evidence (*Table 2*) and bias associated with the included studies (see *Appendix 3 – Summary of evidence process*) using the GRADEpro Guideline Development Tool (GRADEpro GDT).[37,38] Where the first clinical question was answered in the negative (i.e., drug is not > 30% renally eliminated, no nephrotoxic potential and/or altered pharmacokinetics/ pharmacodynamics in kidney dysfunction), the remaining clinical questions did not require evidence profiles.

At least two members of the *Content Development Working Group* independently reviewed evidence profiles for each anticancer drug (including their relevant clinical questions),and provided their draft recommendations according to the evidence-to-decision framework in the GRADEpro GDT (see *Appendix 4 – Evidence-to-decision framework*).[38]

Each anticancer drug was presented to a panel discussion (involving selected members from the *Content Development Working Group* and additional invited expert clinicians), where draft recommendations were reviewed and refined for clinical practicality. The strength of each recommendation was reflected in its wording *(Table 3*).[37] In the absence of published evidence, expert opinion/clinical consensus was proposed for recommendations widely considered as sound practice by the panel discussion members.

Anonymous voting was conducted on the final drug recommendations by the entire *Content Development Working Group* to achieve consensus.

Table 2 – Levels of evidence certainty/quality[37]

Certainty/Quality	Definition
High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.
Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.
Low	This research provides some indication of the likely effect, however, the likelihood that it will be substantially different (a large enough difference that it might have an effect on a decision) is high.
Very low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different (a large enough difference that it might have an effect on a decision) is very high.

Table 3 – Strength of evidence and the implications of the recommendation[37]

Strength	Implications	
	Patients	***Clinicians***
Strong "*We recommend*"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.
Conditional "*We suggest*"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.

Results

Part 1 – General ADDIKD recommendations

The workshop involved 56 participants from the Asia-Pacific region, Europe, and North America. The three recommendations achieved > 80% consensus at the workshop, enabling further progression of *ADDIKD* to Part 2. The participants discussed the practicality of the standardised approach to assessing kidney function for different clinical situations and exceptions when applied to anticancer drug dosing.

Part 2 – Drug-specific ADDIKD recommendations

A review of 2263 published articles and 177 registered product information monographs enabled 127 GRADE evidence profiles to be assessed by the *Content Development Working Group*, resulting in evidence- and consensus-based dosing recommendations for 59 anticancer drugs. Ten panel discussions enabled the further refinement of the recommendations.

When interpreting the certainty/quality of evidence and strength of the recommendations, the *Content Development Working Group* and additional invited experts for the panel discussion considered:

- The quality and quantity of evidence
- The balance between benefits and harms associated with the anticancer drug in kidney dysfunction
- The magnitude of effect, feasibility, and accessibility of any dose adjustment
- Whether there was data on critical outcomes (i.e., overall survival, grade ≥ 3 adverse events), with or without dose adjustment.

As this subject area contained many small observational studies rather than large randomised controlled trials, the GRADE approach categorised the certainty of evidence to be low in most circumstances. When no studies existed, this was reflected in the certainty of evidence for the recommendation, or clinical consensus was achieved. The panel discussion made consensus decisions where evidence was sparse and/or conflicting.

Practice points were included for certain anticancer drugs to highlight additional considerations when administering the drug in kidney dysfunction (e.g., preventative

and supportive care measures).

'Quick reference' dosing tables incorporated a traffic light system to provide clinicians with a visual alert around certain levels of kidney function or to consider specific patient risk factors (*Figure 1*).

Final voting by the entire *Content Development Working Group* achieved ≥ 70 % acceptance on the finalised drug-specific recommendations and dosing tables.

Figure 1 - Example of a dose recommendations table according to kidney function

Green – "go" – proceed with full dose

Yellow – "wait" - dose adjustment, closer monitoring for drug-related adverse events and/or special cautions to consider

Red – "stop" - do not proceed.

ANTICANCER DRUG DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**full dose**	Increased risk of adverse events.
30 – 44	**reduce by 25%** [a,b] **or alternative protocol**	Consider a 25% dose reduction in patients with *either*: • non-curative treatment intent • concomitant nephrotoxic drug exposure • a poor performance status. In all other patients, consider a clinically appropriate alternative treatment protocol Increased risk of adverse events.
15 – 29	**AVOID**	Not recommended – use a clinically appropriate alternative treatment protocol.
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

[a] Dose adjustment may require rounding to nearest capsule strength to enable delivery of a measurable dose.
[b] The dose reduction applies to each individual dose and not to the total number of days or duration within the treatment cycle.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

Footnotes with drug specific practice points

General recommendations

Kidney function assessment in adult cancer patients

RECOMMENDATION 1

We recommend the use of estimated glomerular filtration rate calculated via the Chronic Kidney Disease – Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$) equation to guide the assessment of kidney function, except where directly measured glomerular filtration rate (mGFR) is clinically necessary.

Evidence quality/certainty: ***clinical consensus****; strength of recommendation:* ***strong****.*

1.1. The most accurate method of assessing kidney function in adult cancer patients is by directly mGFR.

Directly mGFR, expressed in mL/min, refers to a direct measurement of the CL of exogenous markers (filtered by the glomerulus and neither reabsorbed nor secreted by the kidney tubules), such as iohexol, iothalamate, ^{51}Cr-EDTA or ^{99m}Tc-DTPA.[20,39] The accessibility, time and cost of directly mGFR often makes it impractical in clinical settings where estimation of GFR is more readily available.

1.2. $eGFR_{CKD\text{-}EPI}$ is the preferred method for *estimating* kidney function in adult cancer patients because:

- it is more accurate and precise than other estimation methods. **$eGFR_{CKD\text{-}EPI}$** is more precise than CrCl calculated via the Cockcroft-Gault equation, with 84% versus 74% accuracy of values within 30% of directly mGFR.[26] Although using identical variables, the CKD-EPI equation performs slightly better than the MDRD equation at aligning with risk stratification categories for CKD-related outcomes.[40,41] and when eGFR > 60 mL/min/1.73 m^2.[42]

- it accounts for the international standardisation of the creatinine assay.[43-45] The Cockcroft-Gault equation was developed using non-standardised creatinine assays,[22] and therefore CrCl calculations should be cautiously interpreted in the context of current kidney dysfunction categories.[46]

- it has been tested and validated in diverse populations (including cancer patients).[46-49] The Cockcroft-Gault equation was derived from a small, hospitalised, mostly male, Caucasian population.[22,50]

- it is automatically reported in laboratory results when requesting S_{Cr} measurement in many countries (as per recommendations from KDIGO,[11] National Kidney Foundation,[51] National Institute for Health and Care Excellence,[52] and Australasian Creatinine Consensus Working Group[44]), enabling ease of use at both the patient bedside and outpatient clinic.

- it aligns with internationally accepted recommendations from KDIGO and enables classification of kidney function as per the KDIGO CKD categories.[27]

The **CKD-EPI equation** predicts kidney function using the variables of age, sex, S_{Cr}, and, where applicable, race (the 2009 version of the equation allows for an extra coefficient to account for individuals of African American ancestry having higher S_{Cr} compared to individuals of non-African American ancestry).[26] Outside of North America, the CKD-EPI 2009 equation has been largely implemented in clinical practice without the race coefficient.[44,52] In 2021, the National Kidney Foundation and American Society of Nephrology Task Force recommended refitting the CKD-EPI 2009 equation without race, citing that race was a social rather than a biological construct.[53] eGFR calculated with the refitted equation delivered more precision to directly mGFR with individuals who previously used the race coefficient, but overestimated eGFR by ~ 3.9 mL/min/1.73 m^2 in other populations.[54]

$eGFR_{CKD\text{-}EPI}$ is indexed to a standardised body surface area (BSA) of 1.73 m^2 to enable comparison of kidney function between individuals with different body sizes with the assumption that BSA is a reliable indicator of kidney size.[26,55] The applicability of the BSA reference value of 1.73 m^2 to the larger-sized contemporary population has been questioned.[56,57]

Within *ADDIKD*, **$eGFR_{CKD\text{-}EPI}$** refers to estimated GFR calculated via the CKD-EPI 2009 equation without the race coefficient and standardised for BSA.

For females:

- when serum creatinine (S_{Cr}) ≤ 62 µmol/L

$$eGFR\ (mL/min/1.73\ m^2) = 144 \times (S_{Cr} \times 0.0113/0.7)^{-0.329} \times (0.993)^{age}$$

- when S_{Cr} > 62 µmol/L

$$eGFR\ (mL/min/1.73\ m^2) = 144 \times (S_{Cr} \times 0.0113/0.7)^{-1.209} \times (0.993)^{age}$$

For males:

- when S_{Cr} ≤ 80 µmol/L

$$eGFR\ (mL/min/1.73\ m^2) = 141 \times (S_{Cr} \times 0.0113/0.9)^{-0.411} \times (0.993)^{age}$$

- when S_{Cr} > 80 µmol/L

$$eGFR\ (mL/min/1.73\ m^2) = 141 \times (S_{Cr} \times 0.0113/0.9)^{-1.209} \times (0.993)^{age}$$

An online calculator for determining $eGFR_{CKD\text{-}EPI}$ and BSA-adjusted $eGFR_{CKD\text{-}EPI}$ is available via the eviQ website.

1.3. Use $eGFR_{CKD\text{-}EPI}$ results obtained as close as possible to the time of administering the anticancer drug(s) to ensure it is a reflective estimation of the patient's steady state kidney function.

Kidney function assessment is advised at the beginning of anticancer drug treatment (first cycle) and should be considered prior to subsequent cycles of anticancer drug treatment, especially if:

- the anticancer drug dose is guided by kidney function. Approximately 79% of patients undergoing anticancer drug treatment receive at least one anticancer drug that requires dose adjustment for kidney dysfunction.[4,13]
- the anticancer drug demonstrates nephrotoxic potential. Over 80% of cancer patients receive at least one anticancer drug with significant nephrotoxic potential.[58,59]
- the patient has experienced acute illness in the previous cycle of treatment or during the current cycle.
- the patient does not have stable kidney function (i.e., treatment of urinary obstruction or renal involvement of malignancy [e.g., multiple myeloma]) or is possibly developing AKI. Up to 27% of cancer patients will develop AKI during anticancer drug treatment, with 7 – 10% requiring KRT.[6,7,60] Contributing factors include drug-related AKI, sepsis, hypovolaemia, tumour lysis syndrome (TLS) and urinary tract obstruction.[6,7,60]

Using S_{Cr}-based estimates such as $eGFR_{CKD\text{-}EPI}$ require kidney function to be at steady state. $eGFR_{CKD\text{-}EPI}$ should be interpreted cautiously in the acutely ill or patients who demonstrate rapidly changing kidney function, noting that peaks in S_{Cr} can lag 24 – 72 hours after kidney injury.[61]

Consider performing a second $eGFR_{CKD\text{-}EPI}$ prior to initiating anticancer drug treatment if:

- the clinical state of the patient has changed since the most recent $eGFR_{CKD\text{-}EPI}$ result, or there is a suspicion of declining kidney function
- the last reported $eGFR_{CKD\text{-}EPI} < 60$ mL/min/1.73 m^2 and the dose of the intended anticancer drug(s) is guided by kidney function.

1.4. Clinical situations where calculating $eGFR_{CKD\text{-}EPI}$ may not be reliable[62] include (but are not limited to):

- AKI
  - KDIGO defines AKI as either a rise in S_{Cr} by ≥ 26.5 µmol/L within 48 hours, or a rise in S_{Cr} to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or urine volume < 0.5 mL/kg/hr for 6 hours.[11]
  - Consult the nephrology team if AKI is suspected or kidney function is declining by ≥ 10% per day.
- Volume displacement (e.g., fluid overload, dehydration)
- Obesity
  - Obesity is defined by the World Health Organisation as a body mass index (BMI) ≥ 30 kg/m^2,[63] and is considered a guide, as occasionally it may not always correspond to the same body composition in different patients (fat versus lean muscle percentage).
  - In obese patients, the most accurate assessment of kidney function is directly mGFR.[64] In the absence of directly mGFR, estimation methods may be considered for their practicality within the clinical situation, noting their overall inferiority in this cohort.
  - Estimating CrCl calculated with the Cockcroft-Gault equation and using actual bodyweight as the weight descriptor, overestimates kidney function in obese patients.[65,66] As lean muscle mass does not increase proportionally to actual body weight in obesity,[67] using alternate body weight descriptors (i.e., lean body weight,[65,67] adjusted body weight[59,68]) that correlate more precisely with lean muscle mass (and S_{Cr} production) may result in an improved estimation of kidney function.
  - Studies have shown $eGFR_{CKD\text{-}EPI}$ to underestimate kidney function in obese patients.[65,69] eGFR adjusted for BSA (expressed as mL/min), incorporates body size parameters into the $eGFR_{CKD\text{-}EPI}$ value by removing the 1.73 m^2 standardisation (where individual BSAs are much larger than the 1.73 m^2 indexing). Several studies have demonstrated **BSA-adjusted $eGFR_{CKD\text{-}EPI}$** values are closer to mGFR than BSA-standardised $eGFR_{CKD\text{-}EPI}$.[49,70,71] However, there are conflicting reports regarding the performance of BSA-adjusted $eGFR_{CKD\text{-}EPI}$ in comparison to CrCl using alternative weight descriptors in this cohort, particularly with BMI > 40 kg/m^2.[65,69]

- Non-obese sarcopenia
  - Due to a loss of skeletal muscle mass in this cohort, S_{Cr}-based calculations may not be useful as it potentially overestimates kidney function.[72]
  - In the absence of directly mGFR,[20] estimations of kidney function may be considered for their practicality within the clinical situation whilst noting the limitations in this population with low muscle mass.
  - Measurement of CrCl using 24-hour urine collection may be considered. A disadvantage of this method is the difficulty and practicality of collecting the urine correctly over 24 hours, particularly in an ambulatory patient.
  - Calculation of eGFR using the CKD-EPI equation with serum cystatin C (S_{Cys}) instead of S_{Cr} has demonstrated accuracy in this cohort.[73] A disadvantage of this is the accessibility to perform a S_{Cys} , the complexity of the calculation and the confounding issue of cancer cells which may incidentally produce cystatin C (leading to underestimation of eGFR).[74]
  - BSA-adjusted $eGFR_{CKD\text{-}EPI}$ overestimated kidney function in a study with cachexic, low muscle mass patients.[75]
- Conditions of skeletal muscle, paraplegia, or amputees
  - Where directly mGFR is impractical to perform, a 24-hour urine collection for measuring CrCl may be useful in guiding kidney function assessment, noting the limitations with collecting an accurate sample.[64,76]
- High muscle mass[77]
- Exceptional dietary intake (e.g., vegetarian diet, high protein diet, creatine supplements) or recent consumption of cooked meat
  - In patients with *exceptional dietary intake* where directly mGFR is unable to be performed, a 24-hour urine collection to measure CrCl may be useful, noting the limitations with collecting an accurate sample.
  - In patients where *recent consumption of cooked meat* may make their eGFR less reliable, although rarely clinically significant, consider re-assessment of $eGFR_{CKD\text{-}EPI}$ after they have fasted or specifically avoided a cooked meat meal within 4 hours of blood sampling.

- Advanced liver disease
  - In liver cirrhosis, S_{Cr} is often affected by muscle wasting and elevated bilirubin interferes with creatinine assays, possibly leading to an overestimation of kidney function.[78-80]
  - Directly mGFR or eGFR using S_{Cys}, if accessible and practical, have been utilised for kidney function assessment in cirrhosis.[81,82]
  - CrCl measured with a 24-hour urine collection may be appropriate in this cohort,[83] whilst noting the limitations with collecting an accurate sample.
- Untreated hypothyroidism[84]
- Drugs interfering with creatinine secretion in renal proximal tubules (e.g., olaparib,[85] trimethoprim[86]) or the creatinine assay (e.g., flucytosine[87]). If this is not newly initiated drug treatment, is it unlikely to be of clinical significance.
- Ureteric obstruction and timing/place of stent[88,89]
- Transgender population
  - Sex coefficients in the CKD-EPI formula have not been validated in transgender people and the role of gender-affirming hormone therapy on eGFR is uncertain.[90,91] Until validation studies are performed, calculation of $eGFR_{CKD\text{-}EPI}$ using both male and female coefficients is advised to indicate the range of kidney function in transgender persons on gender-affirming hormone therapy.[91]
  - In clinical situations where a more accurate assessment of kidney function is required, a directly mGFR is advised.[91]

1.5. Clinical situations where $eGFR_{CKD\text{-}EPI}$ is unsuitable for assessing kidney function[44,62]:

- Pregnancy
- Patients < 18 years of age
- KRT

Application of kidney function assessment to guide dosing of anticancer drugs

RECOMMENDATION 2

We recommend estimated glomerular filtration rate calculated via the Chronic Kidney Disease – Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$) equation to guide the dosing of anticancer drugs whose dose is dependent on kidney function, except in specific clinical situations or for a select group of anticancer drugs where $eGFR_{CKD\text{-}EPI}$ may be unsuitable.

Evidence quality/certainty: ***clinical consensus****; strength of recommendation:* ***strong****.*

Approximately 15 – 20% of patients with cancer have an eGFR 30 – 59 mL/min/1.73 m^2,[4,13] a kidney function range where many anticancer drugs have pre-defined dose adjustments or exclusions.[92,93] Accurate kidney function assessment is of particular importance in this cohort as small variations in kidney function may place patients in CKD categories that preclude them from receiving drug therapy or at thresholds for significant dose adjustments.

The European Medicines Agency (EMA)[94] and the United States Food and Drug Administration (FDA)[95] guidelines on drug development submissions in kidney dysfunction recommend GFR for the assessment of kidney function, with EMA specifically recommending directly mGFR, whilst the FDA endorses BSA-adjusted eGFR alongside CrCl as options. However, early drug development studies investigating renal drug CL require further consideration, as eGFR (including BSA-adjusted eGFR) and CrCl, unlike directly mGFR, may not adequately capture changes to renal CL with drugs that undergo extensive tubular secretion.[58,96]

Although CrCl calculated via the Cockcroft-Gault has been used historically to guide dosing in kidney dysfunction, it lacks applicability to current anticancer drug dosing as older studies estimated CrCl using non-standardised creatinine assays.[46] Certainly in carboplatin and cisplatin, $eGFR_{CKD\text{-}EPI}$ demonstrates more precision than CrCl in assessing kidney function for drug dosing.[97]

If CrCl in certain circumstances is utilised instead of $eGFR_{CKD\text{-}EPI}$ or directly mGFR, it may be judiciously applied to guide dose adjustments described in *ADDIKD's Drug specific recommendations.* Comparisons of eGFR versus CrCl predictions in patients

receiving non-cancer drugs have suggested that 88% of patients with kidney dysfunction did not have a change in dose regardless of the estimation method.[98]

2.1 Clinical situations where an alternative to $eGFR_{CKD\text{-}EPI}$ may be preferred to guide dosing of anticancer drugs:

- A select group of anticancer drugs including, but not limited to, carboplatin, cisplatin, and methotrexate (especially doses ≥ 500 mg/m^2). In these drugs, directly mGFR is recommended for at least the initial dose (see *Drug specific recommendations)*
- Extremes of body weight/composition (obesity, sarcopenia)
- Exceptional dietary intake (e.g., vegetarian diet, high protein diet, creatine supplements), conditions of skeletal muscle, paraplegia, or in amputees.

> For additional clinical situations where alternatives to $eGFR_{CKD\text{-}EPI}$ may be preferred, refer to ***where eGFR may be unreliable*** *(see Recommendation 1.4)*.

2.2 BSA-adjusted $eGFR_{CKD\text{-}EPI}$ is not routinely advised to guide dosing of anticancer drugs over standardised $eGFR_{CKD\text{-}EPI}$ within *ADDIKD*, except for carboplatin.

Anticancer drug dosing based on weight descriptors (e.g., BSA, weight) may impact the performance of BSA-adjusted $eGFR_{CKD\text{-}EPI}$ (expressed as mL/min) to guide dosing, as body size/composition will be accounted for twice to individualise doses.[56,57,99,100] When dosing capecitabine in mg/m^2 and utilising BSA-adjusted $eGFR_{CKD\text{-}EPI}$ to determine dose adjustments in kidney dysfunction, patients with a lower BSA were underdosed and conversely those with a larger BSA were overdosed, despite both groups having the same standardised $eGFR_{CKD\text{-}EPI}$.[101] Aminoglycosides dosed in mg/kg, found that BSA-adjusted $eGFR_{CKD\text{-}EPI}$-guided dosing was less precise than standardised $eGFR_{CKD\text{-}EPI}$ in predicting drug CL in overweight and obese patients.[102] The CL of ganciclovir (dosed in mg/kg) correlated similarly with standardised and BSA-adjusted $eGFR_{CKD\text{-}EPI}$ in patients without extremes of body size.[103]

2.3 BSA-adjusted $eGFR_{CKD\text{-}EPI}$ is a suitable alternative to directly mGFR for use in the Calvert formula when dosing carboplatin in specific circumstances.

For carboplatin dosing, BSA-adjusted $eGFR_{CKD\text{-}EPI}$ (expressed as mL/min) in the Calvert formula, demonstrates more precision towards directly mGFR than standardised $eGFR_{CKD\text{-}EPI}$,[49,71] and is a suitable alternative when directly mGFR is unavailable in specific circumstances (see *Carboplatin dose recommendations*).

2.4 When dosing anticancer drug treatment in the presence of kidney dysfunction, carefully consider the patient's clinical status, comorbidities, treatment protocol, beliefs/attitudes towards treatment, anticancer drug properties, concomitant medicines, accessibility to directly mGFR, and the evidence and strength behind dose recommendations.

A pragmatic approach to dosing in kidney dysfunction is essential when applying kidney function estimations to adjust anticancer drug doses, by accounting for drug and patient factors and assessing the clinical risk-benefit of administering a particular dose. See *Considerations when treatment is planned in the presence of kidney dysfunction* for details.

Considerations when treatment is planned in the presence of kidney dysfunction

1. Clinical status of the *patient*
    - Are they acutely unwell?
    - Are there cancer-related factors contributing to their kidney dysfunction (e.g., multiple myeloma, tumour causing urinary obstruction, tumour infiltration into renal parenchyma)?
    - Are there other circumstances potentially impacting their kidney function (e.g., presence of a singular or horseshoe kidney, transplanted kidney, dialysis)?
    - Do they display symptoms of dehydration or fluid overload?
    - What is their performance status?
    - Are there comorbidities that have been already accounted for in dosing of the anticancer drug (e.g., age-adjusted cytarabine which primarily compensates for the age-related decline in kidney function)?
    - Are there additional comorbidities that may influence the delivery of anticancer drugs (e.g., liver dysfunction may alter non-renal or renal

elimination pathways of drugs)?
    - Are there clinically relevant pharmacogenetics that will impact dosing?
    - Are they hypoalbuminaemic and will this change exposure to the anticancer drug if it is highly protein bound?
    - Are they fluid restricted as part of their kidney dysfunction therapy, and will this affect the safe administration of the anticancer drug?

2. What are the patient's attitudes or beliefs towards their anticancer drug treatment?

3. Curative or non-curative intent of anticancer drug treatment and the potential for dose adjustments to alter therapeutic efficacy of the treatment protocol.

4. Drug *pharmacokinetics* (effect of the body on the drug – absorption, distribution, metabolism, and excretion) and *pharmacodynamics* (effect of drug on the body). Not every drug in a treatment protocol may require a dose adjustment in kidney dysfunction, but there should be careful consideration of drugs with a narrow therapeutic window as minor changes in kidney function and/or dose adjustments may have a clinically significant effect on drug exposure.

5. The suitability of clinically appropriate treatment protocols with similar efficacy and without drugs dependent on kidney function for dosing.

6. Concomitant nephrotoxic drugs (including over-the-counter and complementary/alternative medicines) that may increase risk of AKI and the subsequently increase the potential for adverse events caused by the anticancer drug (see *Appendix 5 – Nephrotoxic anticancer drugs*).

7. What is the risk of TLS occurring in this patient with the proposed treatment protocol?
    - Cancer-related risk factors include malignancies with a rapid rate of cell turnover, large tumour burden/bulky disease or highly sensitive to anticancer treatment (i.e., aggressive lymphomas, acute leukaemia, chronic lymphocytic leukaemia [CLL]).[104,105]
    - Pre-existing kidney dysfunction is a major risk factor for the development of TLS.[106], and elevates patients at intermediate risk to the high risk category.[107] Other patient-related factors include oliguria, dehydration, pre-existing hyperuricaemia, and concomitant nephrotoxic drug exposure.[104,105,108]
    - Treatment-related risk factors include the intensity and type of anticancer drug treatment (especially novel targeted agents). [104,105]

Drugs with reported TLS include, but are not limited to, venetoclax,[109] lenalidomide,[109] obinutuzumab,[109] rituximab,[110] and bortezomib.[111,112]

- Adequate preventative and supportive care measures (as per local institutional protocols) are advised to minimise intermediate and high risk TLS (e.g., intravenous hydration, early administration of anti-hyperuricaemics, close laboratory and clinical monitoring for TLS).[105,113]

8. What is the risk of other severe drug-related adverse events with the proposed treatment protocol?

9. Doses of anticancer drugs vary depending on factors other than kidney function, including treatment indications, use as monotherapy or in combination, and intended clinical outcomes. Although ***ADDIKD's*** *Drug specific recommendations* have attempted to include the extensive scope of these drugs by distinguishing dose adjustments at several dosing levels, the guideline for individual drugs may not be applicable in every treatment scenario.

10. Availability of therapeutic drug monitoring (TDM) of the anticancer drug(s). If available, TDM can be useful to ascertain appropriateness of dose adjustments in kidney dysfunction, especially in unusual clinical situations (e.g., extremes of body weight/composition), and guide dosing for subsequent cycles. For further information on the use of TDM in clinical practice, refer to local guidelines and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology.

11. Dose adjustments of oral or parenterally administered anticancer drugs may require rounding to enable delivery of a measurable dose (e.g., oral formulations may need rounding to the nearest available tablet/capsule strength, parenteral formulations may need rounding to a measurable amount for a syringe and/or addition to an intravenous fluid bag).

12. When considering the administration of nephrotoxic anticancer drugs in a patient with kidney dysfunction, pre-existing comorbidities, and/or a degree of proteinuria, consulting the nephrology team is reasonable.

13. Availability of directly mGFR to assess kidney function.

14. The strength of the recommendation and the quality/certainty of evidence (including the paucity in evidence for some drugs) [see *Methods*].

RECOMMENDATION 3

We recommend the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD)[27] categories to guide the stepwise dose adjustment of anticancer drugs in kidney dysfunction and the monitoring of drug-related adverse events.

Evidence quality/certainty: ***clinical consensus****; strength of recommendation:* ***strong****.*

There are limited studies assessing the application of KDIGO CKD categories[27,114,115] (see *Table 4*) in the dose adjustment of anticancer drugs and the monitoring of drug-related adverse events. However, clinical consensus is that standardisation of kidney dysfunction classification across clinical settings reduces complexity of kidney function estimation and promotes uniformity to guide decision making.

In the *ADDIKD* guideline:

- kidney dysfunction is defined as eGFR < 60 mL/min/1.73 m^2
- eGFR refers to $eGFR_{CKD\text{-}EPI}$ within the *Drug specific recommendations.*

Table 4 – KDIGO kidney function categories based on measured/estimated glomerular filtration rate [27,115]

GFR stage	GFR (mL/min/1.73 m^2)	Description of kidney function
G1	≥ 90	Normal or high GFR
G2	60 – 89	Mildly decreased GFR
G3A	45 – 59	Mildly-moderately decreased GFR
G3B	30 – 44	Moderately-severely decreased GFR
G4	15 – 29	Severely decreased GFR
G5	< 15	Kidney failure without KRT
G5D	< 15	Kidney failure with KRT

Abbreviations: GFR – glomerular filtration rate; KDIGO – Kidney Disease Improving Global Outcomes; KRT – kidney replacement therapy

Drug specific recommendations

Anticancer drugs and their dosing in kidney dysfunction

4.1 Azacitidine

RECOMMENDATION 4.1.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous and subcutaneous azacitidine in all cancers. Kidney function may inform the monitoring of adverse events.

Azacitidine is extensively metabolised, primarily via spontaneous hydrolysis and deamination by cytidine deaminase. Azacitidine and its metabolites are predominantly excreted by the kidneys (~ 69 – 91% of total radioactivity recovered in urine), although < 2% is excreted in the urine as unchanged drug.[116-119]

Whilst there are no major differences in azacitidine pharmacokinetics between eGFR 30 – 60 mL/min/1.73 m^2 and eGFR > 60 mL/min/1.73 m^2,[120] reduced azacitidine CL, V_d and increased plasma exposure (AUC) has been observed when eGFR < 30 mL/min/1.73 m^2.[117,120,121]

Evidence for the association between azacitidine-related adverse events and kidney function is conflicting. Several studies have observed no clinically significant difference in the frequency of azacitidine-related adverse events (i.e., myelosuppression, infection, fatigue, vomiting) between patients with (including eGFR < 30 mL/min/1.73 m^2) and without kidney dysfunction receiving full dose.[117,122,123] A retrospective study, however, described a significant correlation between eGFR < 45 mL/min/1.73 m^2 and death from haemorrhage or cardiovascular adverse events with azacitidine treatment.[124] A non-significant trend for more frequent dose reductions and more pronounced decreases in leucocytes, neutrophils and platelets has been reported with eGFR < 30 mL/min/1.73 m^2 (including patients requiring KRT),[117,121,125-127] however this may reflect cancer severity rather than drug toxicity. Case reports describing the initiation of full dose (75 mg/m^2/day) azacitidine in patients with eGFR < 15 mL/min/1.73 m^2 on KRT have demonstrated no treatment-limiting adverse events, although subsequent dose adjustments, febrile neutropenia, and thrombocytopenia and anaemia requiring blood transfusions were observed.[125-127]

Renal adverse events (i.e., renal tubular acidosis, electrolyte abnormalities particularly alterations in bicarbonate serum concentration, AKI), although rare, have been reported with azacitidine treatment.[122,125,128,129] The effect of baseline kidney dysfunction on the risk of azacitidine-related renal adverse events is unclear.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.1.2

We suggest the use of KDIGO CKD categories to guide monitoring for intravenous and subcutaneous azacitidine-related adverse events in kidney dysfunction.

A small number of studies have applied KDIGO CKD categories to guide the monitoring of azacitidine-related adverse events.[122,125] Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.1.3

We suggest *against* an initial dose reduction of intravenous and subcutaneous azacitidine in kidney dysfunction.

The therapeutic efficacy of azacitidine appears to be influenced by baseline kidney function, although the mechanism is unclear. In patients with eGFR < 45 mL/min/1.73 m^2 initiated on full dose azacitidine, significantly inferior overall survival and lower rates of complete and partial response were observed compared to patients with eGFR ≥ 45 mL/min/1.73 m^2.[124] Another study reported decreasing eGFR as an independent predictor of inferior overall survival with azacitidine treatment,[125] with a non-significant reduction in complete response rates in patients with eGFR 30 – 59 mL/min/1.73 m^2 compared to eGFR > 60 mL/min/1.73 m^2.[122] Similarly, in a small retrospective study, complete or partial responses were not achieved among patients with eGFR < 30 mL/min/1.73 m^2 receiving azacitidine treatment.[125]

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose azacitidine. This is based on similar pharmacokinetics[120] and adverse event profiles in patients with eGFR 30 – 59 mL/min/1.73 m^2 compared to patients with eGFR ≥ 60 mL/min/1.73 m^2 initiated on full dose azacitidine.[122,123]

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose azacitidine given the absence of definitive evidence for the impact of dose reductions on survival outcomes and response rates in this setting. Close monitoring for adverse events (i.e., haematological toxicities [myelosuppression], infection, cardiac and vascular adverse events [including haemorrhage], renal adverse events) is advised, especially given the evidence of higher azacitidine systemic exposure[117,120,121] and possible increased severity of toxicities in eGFR < 30 mL/min/1.73 m^2.[117,121,124-127]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 5 – Azacitidine dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS and SUBCUTANEOUS AZACITIDINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>full dose</td><td>Increased risk of adverse events (i.e., haematological toxicities [myelosuppression], infection, cardiac and vascular adverse events [including haemorrhage], renal adverse events).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.2 Bendamustine

RECOMMENDATION 4.2.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous bendamustine in all cancers. Kidney function may inform the monitoring of adverse events.

Bendamustine is extensively metabolised, primarily via non-enzymatic hydrolysis, and has low renal excretion (< 10% of the administered dose is recovered in the urine as unchanged bendamustine and active metabolites).[130-132]

Bendamustine pharmacokinetics do not appear to be influenced by kidney function (including eGFR < 15 mL/min/1.73 m^2), with comparable plasma exposure (AUC, C_{max}) and CL in patients with and without kidney dysfunction.[131,133,134] Although bendamustine is highly protein bound (~ 95%) mostly to albumin, pharmacokinetic parameters are not significantly affected by low serum albumin levels.[134]

Bendamustine appears to be well tolerated in patients with eGFR < 60 mL/min/1.73 m^2.[135-139] A small retrospective study, however, observed a higher incidence of grade ≥ 3 anaemia, leucopenia, neutropenia and infection in patients with eGFR < 15 mL/min/1.73 m^2 receiving bendamustine in combination with bortezomib and prednisone for multiple myeloma.[137] Additionally, in non-Hodgkin lymphoma, a 2.5-fold higher incidence of bendamustine-related grade ≥ 3 thrombocytopenia was observed with eGFR < 40 mL/min/1.73 m^2 compared to patients with eGFR ≥ 60 mL/min/1.73 m^2.[136]

Evidence quality/certainty: ***low****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.2.2

We suggest the use of KDIGO CKD categories to guide monitoring for intravenous bendamustine-related adverse events in kidney dysfunction.

A small number of studies have applied KDIGO CKD categories to the guide monitoring of bendamustine-related adverse events.[137,138] Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.2.3

We suggest *against* an initial dose reduction of intravenous bendamustine in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, full dose bendamustine is suggested due to the lack of significant changes in pharmacokinetics in this cohort compared to eGFR ≥ 60 mL/min/1.73 m^2.[131,133,134]

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to administer full dose bendamustine, given the lack of substantial evidence to suggest a dose reduction will result in a reduced risk of adverse events without compromising therapeutic efficacy. Although pharmacokinetic data when eGFR < 30 mL/min/1.73 m^2 is limited,[131] small cohort studies have demonstrated that full dose bendamustine is well tolerated, with no dose limiting toxicities.[135-139] Close monitoring for adverse events (i.e., haematological toxicities [myelosuppression], infection) is advised given the possible increased incidence of grade ≥ 3 haematological toxicities.[136,137,139]

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 6 – Bendamustine dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS BENDAMUSTINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td rowspan="2">full dose</td><td rowspan="2">Increased risk of adverse events (i.e., haematological toxicities [myelosuppression], infection).</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.3 Bevacizumab

RECOMMENDATION 4.3.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous bevacizumab in all cancers. Kidney function may inform the monitoring of adverse events.

Bevacizumab has a large molecular weight (~ 149 kDa) and therefore is unlikely to undergo glomerular filtration or urinary excretion.[140] Proteolytic catabolism via the reticuloendothelial system is the primary mechanism of bevacizumab metabolism and elimination.[140]

The pharmacokinetics (CL, V_d, AUC) of bevacizumab do not appear to be significantly influenced by kidney function (including when eGFR < 15 mL/min/1.73 m^2).[141-143] Although bevacizumab CL is increased in patients with low serum albumin,[141-143] it is little of clinical significance as bevacizumab is > 98% bound to vascular endothelial growth factor.[143]

There is limited published evidence regarding the effects of kidney dysfunction on the clinical outcomes of bevacizumab treatment. Renal adverse events (i.e., AKI, proteinuria and/or nephrotic syndrome, hypertension, glomerulonephritis, thrombotic microangiopathy) have been reported with bevacizumab treatment.[144-161] An increased incidence of bevacizumab-related renal adverse events has been correlated with higher dosing (≥ 10 mg/kg per dose),[161] increased number of cycles (≥ 13 cycles)[156] and pre-existing hypertension.[156] Case studies have reported bevacizumab-related renal adverse events in patients with CKD,[146,158,159] however the association between baseline kidney dysfunction and risk of renal adverse events is unclear.

For eGFR < 60 mL/min/1.73 m^2, full dose bevacizumab is suggested. Close monitoring for the development of renal adverse events is advised.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice point

- Baseline urinalysis is advised, before commencement and as clinically indicated throughout bevacizumab treatment to monitor for the development of proteinuria.[140,162]

Evidence quality/certainty: ***high****; strength of recommendation:* ***conditional****.*

Table 7 – Bevacizumab dose recommendations according to kidney function

INTRAVENOUS BEVACIZUMAB DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**full dose**	Potential for increased risk of renal adverse events (i.e., AKI, proteinuria and/or nephrotic syndrome, hypertension, glomerulonephritis, thrombotic microangiopathy).
30 – 44		
15 – 29		
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.4 Bleomycin

RECOMMENDATION 4.4.1

We recommend the use of kidney function to inform the initial dosing of intravenous and intramuscular bleomycin in all cancers. Kidney function may inform the monitoring of adverse events.

Bleomycin undergoes intracellular enzymatic inactivation by bleomycin hydrolase in various tissues including in the liver, spleen and kidneys.[163,164] It is primarily renally cleared with ~ 63 – 80% of the administered dose excreted in the urine.[163-168]

Kidney dysfunction (eGFR < 35 mL/min/1.73 m^2) is associated with significantly reduced bleomycin CL, prolonged elimination $t_{1/2}$ and increased systemic exposure (AUC).[165-167,169-173] Reduced renal elimination has also been observed (< 20% of the administered dose excreted in urine), suggesting there may be an increased dependence on non-renal CL in kidney dysfunction.[165,167,169,170,172] More pronounced pharmacokinetic changes (CL, $t_{1/2}$, AUC) have been observed in patients with eGFR < 15 mL/min/1.73 m^2, with up to a 12-fold increase in $t_{1/2}$, and a 10-fold increase in AUC reported, relative to patients with normal kidney function.[165,166,171,173]

Reduced kidney function is significantly associated with an increased risk of serious and potentially fatal bleomycin-induced pulmonary toxicity.[174-176] In patients with eGFR < 25 mL/min/1.73 m^2, there is also an increased risk of other bleomycin-related adverse events (i.e., dermatological toxicities [skin rash], gastrointestinal toxicities [mucositis, nausea and vomiting]) compared with normal kidney function.[173]

Renal adverse events (i.e., thrombotic microangiopathy), although rare, have been reported with bleomycin treatment in combination with other anticancer drugs.[177] The effect of baseline kidney dysfunction on the risk of bleomycin-related renal adverse events is unclear.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

RECOMMENDATION 4.4.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous and intramuscular bleomycin in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of bleomycin and the monitoring of adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.4.3

We recommend an initial dose reduction of intravenous and intramuscular bleomycin in kidney dysfunction.

In addition to the following recommendations, given the increased risk of serious and potentially fatal bleomycin-induced pulmonary toxicity, where eGFR < 60 mL/min/1.73 m^2 close monitoring is recommended.[174-176]

For eGFR 45 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose bleomycin, given the absence of definitive evidence for the impact of dose reductions on adverse events and therapeutic efficacy in this setting. There is a paucity of data on the pharmacokinetic changes and clinical outcomes of bleomycin in this cohort compared to patients with eGFR ≥ 60 mL/min/1.73 m^2.

For eGFR 30 – 44 mL/min/1.73 m^2, clinical consensus is to administer full dose bleomycin, given the absence of definitive evidence for the impact of dose reductions on adverse events and therapeutic efficacy in this setting. Additionally, there are no significant changes in bleomycin pharmacokinetics (CL, $t_{1/2}$, AUC) in this cohort compared to eGFR ≥ 60 mL/min/1.73 m^2.[165,170] Where either the intent of treatment is curative, or other risk factors for pulmonary toxicity are present (i.e., age > 60 years, previous mediastinal radiotherapy, high-dose oxygen support, concurrent administration of other anticancer drugs [especially treatment protocols containing cyclophosphamide or vincristine], concomitant nephrotoxic drug exposure or cumulative bleomycin dose > 300 000 IU),[174,177,178] consider a clinically appropriate alternative treatment protocol.

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is for a 25 – 50% dose reduction given the evidence for higher bleomycin systemic exposure[165-167,169-173] and increased incidence and severity of toxicities (i.e., pulmonary toxicity, dermatological toxicities [skin rash], gastrointestinal toxicities [mucositis, nausea and vomiting]).[173-176] It is unclear whether dose adjustment reduces the incidence of bleomycin-related adverse events without compromising therapeutic efficacy. Where either the intent of treatment is curative, or other risk factors for pulmonary toxicity are present (i.e., age > 60 years, previous mediastinal radiotherapy, high-dose oxygen support, concurrent administration of other anticancer drugs [especially treatment protocols containing cyclophosphamide or vincristine], concomitant nephrotoxic drug exposure or cumulative bleomycin dose > 300 000 IU),[174,176,178] consider a clinically appropriate alternative treatment protocol.

For eGFR < 15 mL/min/1.73 m^2, clinical consensus is to avoid bleomycin and use a clinically appropriate alternative treatment protocol. There is a paucity of data in the efficacy of bleomycin in patients with eGFR < 15 mL/min/1.73 m^2, and despite a 50% dose reduction, an increased risk of bleomycin-related adverse events has been observed.[173] There is currently no substantial evidence to suggest a dose reduction of bleomycin in this cohort will reduce the risk of adverse events without compromising therapeutic efficacy.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice point

- The dose reduction applies to each individual dose and not to the total number of days or duration of bleomycin per treatment cycle.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 8 – Bleomycin dose recommendations according to kidney function

INTRAVENOUS and INTRAMUSCULAR BLEOMYCIN DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**full dose**	Increased risk of pulmonary toxicity.
30 – 44	**alternative protocol** **or** **full dose**	Consider a clinically appropriate alternative treatment protocol in patients with *either*: • curative treatment intent • risk factors for pulmonary toxicity (i.e., age > 60 years, previous mediastinal radiotherapy, high-dose oxygen support, concurrent administration of other anticancer drugs, cumulative bleomycin dose > 300 000 IU, concomitant nephrotoxic drug exposure). In all other patients, consider full dose. Increased risk of pulmonary toxicity.
15 – 29	**alternative protocol** **or** **reduce by 25 – 50%** [a]	Consider a clinically appropriate alternative treatment protocol in patients with *either*: • curative treatment intent • risk factors for pulmonary toxicity (i.e., age > 60 years, previous mediastinal radiotherapy, high-dose oxygen support, concurrent administration of other anticancer drugs, cumulative bleomycin dose > 300 000 IU, concomitant nephrotoxic drug exposure). In all other patients, consider a 25 – 50% dose reduction. Increased risk of adverse events (i.e., pulmonary toxicity, dermatological toxicities [skin rash], gastrointestinal toxicities [mucositis, nausea and vomiting]).
< 15 (without KRT)	**AVOID**	Not recommended – use a clinically appropriate alternative treatment protocol.
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

[a] The dose reduction applies to each individual dose and not to the total number of days or duration of bleomycin per treatment cycle.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; IU, international units; KRT, kidney replacement therapy.

4.5 Bortezomib

RECOMMENDATION 4.5.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous and subcutaneous bortezomib in all cancers. Kidney function may inform the monitoring of adverse events.

Bortezomib is primarily metabolised by hepatic cytochrome P450 (CYP450) enzymes to two inactive enantiomers that are further processed and eliminated, both renally and in bile.[179] Renal CL contributes to ~ 26% of bortezomib elimination.[180] Bortezomib pharmacokinetics (CL, $t_{1/2}$ and C_{max}) are not significantly influenced by kidney function, although data is sparse in patients with eGFR < 15 mL/min/1.73 m^2.[180,181]

The effect of kidney dysfunction on the risk of bortezomib-related adverse events is unclear. Whilst many studies have observed a comparable incidence of adverse events in patients with and without kidney dysfunction,[181-189] some studies have reported a higher incidence of grade ≥ 3 bortezomib-related adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia], infections, neurotoxicity [peripheral neuropathy, autonomic neuropathy]), and associated dose reductions and early treatment cessation when eGFR < 30 mL/min/1.73 m^2.[190-192]

Renal adverse events (i.e., AKI, thrombotic microangiopathy, acute interstitial nephritis), although infrequent, have been reported with bortezomib treatment.[193-196] It is unclear whether baseline kidney dysfunction influences the risk of bortezomib-related renal adverse events.

*Evidence quality/certainty: **moderate**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.5.2

We suggest the use of KDIGO CKD categories to guide monitoring for intravenous and subcutaneous bortezomib-related adverse events in kidney dysfunction.

There are a limited number of studies assessing the application of KDIGO CKD categories to guide dose adjustment of bortezomib and the monitoring of adverse events.[190,197] Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.5.3

We suggest *against* an initial dose reduction of intravenous and subcutaneous bortezomib in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, full dose bortezomib is suggested due to the lack of significant changes in pharmacokinetics in this cohort compared to eGFR ≥ 60 mL/min/1.73 m^2.[180,181]

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to administer full dose bortezomib with close monitoring for adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia], infection, neurotoxicity [peripheral neuropathy, autonomic neuropathy]) given the possible increased incidence and severity in this setting.[190-192] There is no substantial evidence that a dose reduction of bortezomib in patients with kidney dysfunction will result in a reduced risk of adverse events without compromising therapeutic efficacy. This is further supported by international consensus recommendations for multiple myeloma where full dose bortezomib is recommended in eGFR < 60 mL/min/1.73 m^2.[198]

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***conditional****.*

Table 9 – Bortezomib dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS and SUBCUTANEOUS BORTEZOMIB DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td rowspan="2">full dose</td><td rowspan="2">Increased risk of adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia], infection, neurotoxicity [peripheral neuropathy, autonomic neuropathy]).</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.6 Cabazitaxel

RECOMMENDATION 4.6.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous cabazitaxel in all cancers. Kidney function may inform the monitoring of adverse events.

Cabazitaxel is primarily eliminated via hepatic metabolism and biliary excretion (76% of the dose excreted in the faeces as numerous metabolites) and < 4% of the dose excreted in the urine (~ 2% as unchanged drug).[199] Cabazitaxel is highly protein bound (92%), mostly to albumin.[200,201]

Kidney function (eGFR range 8 – 101 mL/min/1.73 m^2) does not significantly influence cabazitaxel pharmacokinetics, with comparable plasma exposure (AUC), CL and unbound fraction of cabazitaxel observed in patients with and without kidney dysfunction.[200,201]

Cabazitaxel has not demonstrated a higher incidence of grade ≥ 3 adverse events (i.e., haematological toxicities [febrile neutropenia], gastrointestinal toxicities [diarrhoea]) directly related to kidney dysfunction,[200] although data is sparse when eGFR < 15 mL/min/1.73 m^2. Renal adverse events (i.e., AKI, thrombotic microangiopathy), although rare, have been reported with cabazitaxel treatment, albeit do not appear to be associated with baseline kidney function.[202-204]

For eGFR 15 – 59 mL/min/1.73 m^2, full dose cabazitaxel is recommended.

For eGFR < 15 mL/min/1.73 m^2, full dose cabazitaxel is recommended, with close monitoring for adverse events (i.e., haematological toxicities [febrile neutropenia], gastrointestinal toxicities [diarrhoea]) due to the paucity of data in this setting.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **very low**; strength of recommendation: **strong**.*

Table 10 – Cabazitaxel dose recommendations according to kidney function

INTRAVENOUS CABAZITAXEL DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59		
30 – 44		
15 – 29		
< 15 (without KRT)	**full dose**	Potential for increased risk of adverse events (i.e., haematological toxicities [febrile neutropenia], gastrointestinal toxicities [diarrhoea]).
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.7 Capecitabine

RECOMMENDATION 4.7.1

We recommend the use of kidney function to inform the initial dosing of oral capecitabine in all cancers. Kidney function may inform the monitoring of adverse events.

Capecitabine is a precursor of 5'-deoxy-5-fluorouridine (5'-DFUR), which is activated to the cytotoxic moiety 5-fluorouracil (5-FU) and subsequently converted to inactive metabolites (mainly in the liver by dihydropyrimidine dehydrogenase [DPD]).[205] Capecitabine and its metabolites are primarily excreted in urine (mean urinary recovery of 71 – 87%; 3% as unchanged capecitabine, ~ 62% as an inactive metabolite, 7 – 10% as 5'-DFUR, and < 1% as 5-FU).[205] Polymorphisms in the gene encoding DPD (*DPYD*) may lead to reduced DPD activity, resulting in severe (sometimes fatal) toxicity due to the inability to effectively clear capecitabine's active metabolite, 5-FU.[206]

Kidney dysfunction (eGFR range 15 – 80 mL/min/1.73 m^2) does not significantly influence the systemic exposure (AUC) of capecitabine or 5-FU.[207,208] However, plasma concentrations of 5'-DFUR, which may reflect the tissue exposure to 5-FU most closely,[209] are significantly increased in kidney dysfunction (up to a 35% increase in AUC when kidney function is reduced by 50%).[207,208] Increased AUC of 5'-DFUR has been correlated to an increased incidence of capecitabine-related grade ≥ 3 adverse events.[208,210]

A higher incidence of grade ≥ 3 capecitabine-related adverse events (i.e., gastrointestinal toxicities [diarrhoea, mucositis], dermatological toxicities [palmar-plantar erythrodysesthesia], haematological toxicities, fatigue) and subsequent dose reductions, treatment interruptions and early cessation has been observed in patients with kidney dysfunction (eGFR < 60 mL/min/1.73 m^2) compared to those without.[208-214]

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.7.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral capecitabine in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of capecitabine and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.7.3

We recommend an initial dose reduction of oral capecitabine in kidney dysfunction.

In addition to the following recommendations, close monitoring for adverse events (i.e., gastrointestinal toxicities [diarrhoea, mucositis], dermatological toxicities [palmar-plantar erythrodysesthesia], haematological toxicities, fatigue) is advised where eGFR < 60 mL/min/1.73 m^2. This is given the evidence of higher systemic exposure of metabolites[207,208] and increased incidence of grade ≥ 3 adverse events and associated dose reductions, treatment interruptions and early cessation in kidney dysfunction.[208-214]

For eGFR 45 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose capecitabine as there is limited evidence that a dose reduction will reduce the risk of adverse events without compromising therapeutic efficacy.[215-217] If clinically appropriate, a fluorouracil-containing treatment protocol may be considered as an alternative.

For eGFR 30 – 44 mL/min/1.73 m^2, clinical consensus is that a fluorouracil-containing treatment protocol should be considered first, if clinically appropriate, as an alternative to dose reducing capecitabine. If proceeding with capecitabine, clinical consensus is that a 25% dose reduction may achieve systemic exposure comparable to full dosing in patients with normal kidney function,[208] and potentially reduce the risk of both capecitabine-related haematological adverse events and associated dose adjustments without compromising therapeutic efficacy.[216,218]

For eGFR < 30 mL/min/1.7 3 m^2, due to the sparse and inconsistent evidence for appropriate dose reductions required to reduce the risk of severe treatment-related adverse events whilst maintaining survival outcomes,[209,215,219] clinical consensus is to avoid capecitabine and consider a clinically appropriate alternative treatment protocol.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- *DPYD* genotype testing is advised by regulatory bodies prior to initiating therapy with fluoropyrimidines, as reduced activity of DPD profoundly increases the risk for severe or even fatal toxicities with fluoropyrimidine drugs.[206,220] Doses should be adjusted according to predicted DPD enzyme activity and kidney function.[206,220]

- Consider the twice daily dosing schedule and practicality of tablet strength when applying dose reductions. Dose adjustments may require rounding to nearest tablet strength to enable delivery of a measurable dose.

- The dose reduction applies to each individual dose and not to the total number of days or duration of capecitabine per treatment cycle.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

Table 11 – Capecitabine dose recommendations according to kidney function

ORAL CAPECITABINE DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose** [a]	
45 – 59	**alternative protocol** **or** **full dose** [a]	Consider a clinically appropriate alternative treatment protocol containing **fluorouracil**. If an alternative protocol is not suitable and proceeding with capecitabine, consider full dose. Increased risk of adverse events (i.e., gastrointestinal toxicities [diarrhoea, mucositis], dermatological toxicities [palmar-plantar erythrodysesthesia], haematological toxicities, fatigue).
30 – 44	**alternative protocol** **or** **reduce by 25%** [a,b,c]	Consider a clinically appropriate alternative treatment protocol containing **fluorouracil**. If an alternative protocol is not suitable and proceeding with capecitabine, consider a 25% dose reduction. Increased risk of adverse events (i.e., gastrointestinal toxicities [diarrhoea, mucositis], dermatological toxicities [palmar-plantar erythrodysesthesia], haematological toxicities, fatigue).
15 – 29	**AVOID**	Not recommended – use a clinically appropriate alternative treatment protocol.
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

[a] *DPYD* genotype testing is advised by regulatory bodies prior to initiating therapy with fluoropyrimidines, as reduced activity of DPD profoundly increases the risk for severe or even fatal toxicities with fluoropyrimidine drugs. Doses should be adjusted according to predicted DPD enzyme activity and kidney function.

[b] Consider the twice daily dosing schedule and practicality of tablet strength when applying this dose reduction. Dose adjustments may require rounding to nearest tablet strength to enable delivery of a measurable dose.

[c] The dose reduction applies to each individual dose and not to the total number of days or duration of capecitabine per treatment cycle.

Abbreviations: DPYD, dihydropyrimidine dehydrogenase gene; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.8 Carboplatin

RECOMMENDATION 4.8.1

We recommend the use of kidney function to inform the initial dosing of intravenous carboplatin in all cancers. Kidney function may inform the monitoring of adverse events.

Carboplatin is primarily eliminated through the kidneys, with ~ 32 – 58% of the administered dose excreted unchanged in urine.[221-223]

Carboplatin CL is linearly proportional to kidney function, with renal elimination largely dependent on GFR and a minor reliance on tubular secretion.[224,225] Reduced kidney function significantly decreases urinary elimination, prolongs elimination $t_{1/2}$ and increases AUC of carboplatin.[226-229]

A strong correlation exists between carboplatin AUC, kidney function and the severity of thrombocytopenia, and, to a lesser extent, leucopoenia.[221,230-234] AKI has been occasionally observed in high doses of carboplatin (> 400 mg/m^2), although with less severity than in cisplatin.[235,236]

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong.***

RECOMMENDATION 4.8.2

We recommend *against* the use of KDIGO CKD categories to guide dose adjustment of intravenous carboplatin in kidney dysfunction. We suggest the use of KDIGO CKD categories to guide the monitoring of carboplatin-related adverse events in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories in the dose adjustment of carboplatin and the monitoring of adverse events. We recommend the use of the Calvert formula to dose carboplatin in kidney dysfunction.[221,229] Clinical consensus is to use the KDIGO CKD categories to guide the monitoring of carboplatin-related adverse events.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.8.3

We suggest the use of the Calvert formula with a target AUC to dose intravenous carboplatin in kidney dysfunction in non-transplant settings*.

** For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring carboplatin as part of their treatment. The dose adjustments have not been tailored for these protocols*.

We suggest no reduction in the initial target AUC in kidney dysfunction.

Several studies in patients with reduced kidney function utilised BSA dosing of carboplatin with appropriate dose reductions in eGFR < 60 mL/min/1.73 m^2 but failed to reduce the incidence of treatment-related haematological adverse.[227,230,233,237] Calvert *et al*., demonstrated a target AUC rather than a mg/m^2 dose reduction was more useful in predicting the risk of carboplatin-related toxicity in kidney dysfunction.[221] The development of the Calvert formula,

$$\text{(carboplatin dose (mg) = target AUC (mg mL}^{-1}\text{ min) × [GFR (mL/min) + 25 (mL/min)])}$$

allows individualisation of a carboplatin dose based on a target AUC, renal elimination (GFR) and the constant for non-renal CL (25 mL/min). Applying the Calvert formula to calculate carboplatin doses minimises grade ≥ 3 myelosuppression whilst maintaining therapeutic efficacy in eGFR < 60 mL/min/1.73

m^2.[221,229] Clinical consensus advises:

- Not to further reduce target AUC in kidney dysfunction, as it may compromise clinical benefit.
- Recalculation of carboplatin doses at each cycle is unnecessary, except when baseline kidney function (e.g., eGFR) alters by > 20% or when there is a change in the clinical status of the patient.

Directly measured GFR is the preferred kidney function value in the Calvert formula.

The original Calvert formula study used directly measured GFR.[15] Clinical consensus is that directly measured GFR is the preferred kidney function value when calculating carboplatin doses with the Calvert formula in any kidney function. This is important where there is a curative intent or in clinical situations where estimated kidney function is unreliable for accurate therapeutic dosing, such as when:

- The patient has extremes of body composition (size or muscle mass), conditions of skeletal muscle, is an amputee or is paraplegic
- eGFR ≤ 45 mL/min/1.73 m^2, as estimated kidney function values in the Calvert formula have overestimated kidney function, resulting in higher AUC and increased toxicity[229]
- eGFR > 125 mL/min/1.73 m^2.

If estimating kidney function for use in the Calvert formula, BSA-adjusted eGFR is preferred.

In clinical situations where the decision is made to use estimated kidney function values in place of directly measured GFR, clinical consensus advises using BSA-adjusted eGFR as the kidney function value in the Calvert formula.

$$\text{BSA-adjusted eGFR (mL/min)} = [\text{eGFR (mL/min/1.73 m}^2) \times \text{BSA (m}^2)] \div 1.73$$

AUC calculated using eGFR via the CKD-EPI equation, when adjusted for an individual's BSA (calculated through either DuBois DuBois or Mosteller BSA equations) in the Calvert formula, is more accurate than AUC calculated using CrCl via the Cockcroft-Gault equation.[49,114,238,239]

Kidney function should not be capped at 125 mL/min for use in the Calvert formula.

Capping the kidney function lowers the delivered AUC, resulting in inferior response rates and no significant reduction in toxicities compared to patients receiving doses based on actual kidney function values (even when eGFR > 125 mL/min/1.73 m^2).[240-244] When automated laboratory eGFR values are reported as greater than an upper limit (e.g., eGFR ≥ 90 mL/min/1.73 m^2), manual calculation of a patient's eGFR via the CKD-EPI equation is required before applying this value to the BSA-adjusted eGFR in the Calvert formula.

For eGFR 15 – 59 mL/min/1.73 m^2, there is an increased risk of carboplatin-related adverse events (i.e., thrombocytopenia, leucopenia), especially in patients with either a poor performance status, extensive prior anticancer treatment or concomitant nephrotoxic drug exposure.[235,240] In these situations, increased monitoring for haematological toxicities is advised.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- An online calculator for determining carboplatin doses using BSA-adjusted $eGFR_{CKD\text{-}EPI}$ in the Calvert formula is accessible via the eviQ website.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional***

Table 12 – Carboplatin dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS CARBOPLATIN DOSING RECOMMENDATION [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>target AUC using Calvert formula [b,c]</td><td>Directly measured GFR[d] is the preferred kidney function value in the Calvert formula, especially when either:
treatment intent is curative
patient has extremes of body composition, conditions of skeletal muscle, is an amputee or is paraplegic
eGFR > 125 mL/min/1.73 m².
If estimating kidney function, BSA-adjusted eGFR[e] is preferred as the kidney function value in the Calvert formula.

Capping of kidney function is not recommended[f].</td></tr>
<tr><td>45 – 59</td><td>target AUC using Calvert formula [b,c]</td><td>Directly measured GFR[d] is the preferred kidney function value in the Calvert formula especially when either:
treatment intent is curative
patient has extremes of body composition, conditions of skeletal muscle, is an amputee or is paraplegic.
If estimating kidney function, BSA-adjusted eGFR[e] is preferred as the kidney function value in the Calvert formula.

Increased risk of adverse events (i.e., thrombocytopenia, leucopenia) especially in patients with either a poor performance status, extensive prior anticancer treatment, or concomitant nephrotoxic drug exposure.</td></tr>
<tr><td>30 – 44</td><td rowspan="2">target AUC using Calvert formula [b,c]</td><td rowspan="2">Directly measured GFR[d] is the preferred kidney function value in the Calvert formula.

Increased risk of adverse events (i.e., thrombocytopenia, leucopenia) especially in patients with either a poor performance status, extensive prior anticancer treatment, or concomitant nephrotoxic drug exposure.</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring carboplatin as part of their treatment. The dose adjustments have not been tailored for these protocols.
[b] Recalculation of carboplatin doses at each cycle is unnecessary, except when baseline kidney function (e.g., eGFR) alters by > 20% or when there is a change in the clinical status of the patient.
[c] Calvert formula: dose (mg) = target AUC (mg mL^{-1} min) × [GFR (mL/min) + 25 (mL/min)]
[d] Measured GFR refers to a direct measurement of the clearance of exogenous markers such as iohexol, iothalamate, ^{51}Cr-EDTA (radioactive chromium complex with ethylenediaminetetraacetic acid) or ^{99}Tc-DTPA (TC-diethylenetriaminepentaacetic acid).
[e] BSA-adjusted eGFR (mL/min) via the CKD-EPI equation= [eGFR (mL/min/1.73 m²) × BSA (m²)] ÷ 1.73. Use either Mosteller or DuBois DuBois equations to calculate BSA. Online calculator available at: https://www.eviq.org.au/p/4171
[f] Capping kidney function to 125 mL/min/1.73 m² for use in the Calvert formula may reduce therapeutic efficacy without reducing toxicity. When automated laboratory eGFR values are reported as greater than an upper limit (e.g., eGFR ≥ 90 mL/min/1.73 m²), manual calculation of eGFR via the CKD-EPI equation is required before applying this value to the BSA-adjusted eGFR in the Calvert formula.</td></tr>
<tr><td colspan="3">Abbreviations: AUC, Area under the concentration-time curve; BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate via the CKD-EPI equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.9 Cetuximab

RECOMMENDATION 4.9.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous cetuximab in all cancers.

Cetuximab has a large molecular weight (~ 152 kDa) and is therefore unlikely to undergo glomerular filtration or urinary excretion.[245] Receptor-mediated endocytosis and the reticuloendothelial system are the primary mechanisms of cetuximab elimination.[245]

Cetuximab pharmacokinetics (CL, C_{max}, AUC) do not appear to be significantly influenced by kidney function (including eGFR < 15 mL/min/1.73 m^2, with and without KRT).[246-249]

There is limited published evidence regarding the effects of kidney dysfunction on the clinical outcomes of cetuximab treatment. Case reports in patients with eGFR < 30 mL/min/1.73 m^2 (including patients undergoing KRT), have demonstrated that conventional cetuximab dosing (400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly) was well tolerated, with no grade ≥ 3 or treatment-limiting toxicities.[247,250] Although cetuximab-related renal adverse events (i.e., electrolyte disturbances [hypomagnesaemia], AKI, proliferative glomerulonephritis, nephrotic syndrome, hypoalbuminaemia) have been reported with cetuximab treatment,[250-255] it is unclear whether baseline kidney dysfunction influences the risk of these events occurring.

For eGFR < 60 mL/min/1.73 m^2, full dose cetuximab is recommended.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 13 – Cetuximab dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS CETUXIMAB DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.10 Chlorambucil

RECOMMENDATION 4.10.1

We recommend *against* the use of kidney function to inform the initial dosing of oral chlorambucil in all cancers. Kidney function may inform the monitoring of adverse events.

Chlorambucil is hepatically metabolised to the active phenylacetic acid mustard (PAAM) metabolite, with < 1% of the administered dose excreted in the urine as unchanged chlorambucil or PAAM.[256-258] Chlorambucil is highly protein bound (~99%), mostly to albumin,[256] although the effect of kidney dysfunction on the unbound fraction is unknown.

There is a paucity of data on the effect of kidney dysfunction on chlorambucil pharmacokinetics, however, its elimination appears independent of kidney function (eGFR range 50 – 97 mL/min/1.73 m^2).[259]

There is limited published evidence regarding the effects of kidney dysfunction on clinical outcomes of chlorambucil treatment in cancer populations. Various studies in non-cancer patients with membranous nephropathy and deteriorating kidney function (including eGFR 20 – 59 mL/min/1.73 m^2) have reported serious haematological adverse events with chlorambucil treatment, necessitating dose adjustments and treatment interruptions.[260-263] A case report of chlorambucil treatment for CLL described grade 3 anaemia and thrombocytopenia in a patient with eGFR 16 mL/min/1.73 m^2, necessitating blood transfusions and an interruption to chlorambucil treatment.[264]

For eGFR 45 – 59 mL/min/1.73 m^2, full dose chlorambucil is recommended.

For eGFR 15 – 44 mL/min/1.73 m^2, clinical consensus is for full dose chlorambucil, with close monitoring for adverse events (i.e., haematological toxicities [myelosuppression]) due to the paucity of pharmacokinetic and toxicity data in this setting.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **moderate**; strength of recommendation: **strong**.*

Table 14 – Chlorambucil dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL CHLORAMBUCIL DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="2">full dose</td><td rowspan="2"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td><td rowspan="2">full dose</td><td rowspan="2">Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression])</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.11 Cisplatin

RECOMMENDATION 4.11.1

We recommend the use of kidney function to inform the initial dosing of intravenous cisplatin in all cancers. Kidney function may inform the monitoring of adverse events.

Cisplatin is primarily excreted by the kidneys as unbound free platinum, with ~ 20 – 50% of the administered dose excreted in the urine within 24 hours.[265-270] Cisplatin is highly and irreversibly protein bound (~ 90%) to plasma and tissue proteins, with the rate of excretion largely influenced by the degradation of these proteins and subsequent availability of free platinum.[269]

The effect of baseline kidney function on cisplatin pharmacokinetics is unclear, with some studies demonstrating decreased cisplatin CL and increased AUC with declining kidney function,[269,271] and others concluding no association.[267,272-274] Pharmacokinetic studies inclusive of eGFR < 15 mL/min/1.73 m^2 are lacking. As cisplatin urinary excretion involves both active tubular secretion and reabsorption, the lack of correlation may be a consequence of studies using CrCl estimations that do not account for tubular secretion.[267,268,271,275] Cisplatin CL appears to be associated with dose, frequency of administration (availability of free platinum) and urine flow.[268,271,273,275,276]

Nephrotoxicity is a major dose-limiting adverse event of cisplatin, caused by complex mechanisms primarily involving drug accumulation in the kidneys leading to direct renal cell injury, an inflammatory response, vasoconstriction, and subsequent cell death.[277,2781] Approximately 20 – 30% of patients receiving cisplatin treatment, irrespective of baseline kidney function, will present several days post-dose with a sudden rise in S_{Cr}, sodium and magnesium wasting, and a deficiency in urine concentrating ability.[278] In up to a third of patients, the decline in kidney function is permanent.[279] Risk factors for developing cisplatin-induced renal adverse events include high peaks of free platinum concentrations (possibly caused by doses > 50 mg/m^2, more frequent administration, larger cumulative dose, and hypoalbuminaemia),[267,271,280,281] hypertension,[280,281] concomitant nephrotoxic drug exposure,[282,283] older age (possibly due in part to an age-related decline in kidney function),[281,283] and poor performance status.[282] The effect of baseline eGFR on the risk of cisplatin-associated renal adverse events is unclear, with some studies reporting a correlation[284] and others reporting no relationship between baseline kidney dysfunction and the risk of renal adverse events.[271,281,283,285,286]

For non-renal adverse events, data is sparse in patients with eGFR < 60 mL/min/1.73 m^2.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.11.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous cisplatin in kidney dysfunction.

A small number of studies have applied partial KDIGO CKD categories to guide the dose adjustment of cisplatin and the monitoring of adverse events .[287-292] eGFR was non-inferior to other methods of estimating kidney dysfunction (i.e., CrCl via Cockcroft-Gault equation), when comparing accuracy against directly measured GFR.[97,287,293] Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.11.3

We recommend an initial dose reduction of intravenous cisplatin in kidney dysfunction.

There are a lack of pharmacokinetic studies evaluating cisplatin dose reductions in kidney dysfunction in the non-KRT setting. Several observational studies suggest that cisplatin dose reduction in kidney dysfunction (with the aim to reduce cumulative cisplatin exposure) may decrease the risk of adverse events.[290-292] Patients with eGFR range 30 – 59 mL/min/1.73 m^2 who received a 40 – 50% reduction in cisplatin starting dose showed a comparable incidence of cisplatin-related renal adverse events to those with normal kidney function initiated on full dose (100 mg/m^2).[291,292] Similarly, rates of vomiting, haematological toxicities, and renal adverse events in patients with eGFR range 40 – 59 mL/min/1.73 m^2 receiving a 40 – 70% reduced dose of cisplatin were comparable to those with normal kidney function receiving full dose cisplatin (50 mg/m^2).[290] Fractionating cisplatin doses over several consecutive days does not appear to significantly reduce the incidence of cisplatin-related adverse events (e.g., renal adverse events, haematological toxicities) in kidney dysfunction.[289,294]

The impact of cisplatin dose reduction on therapeutic efficacy is largely unknown due to the exclusion of patients with kidney dysfunction in many clinical trials. Several studies have reported significantly poorer overall survival in patients with eGFR < 60 mL/min/1.73 m^2 who received reduced doses versus patients with normal kidney function receiving full dose (≥ 50 mg/m^2).[289,295,296]

In addition to the following recommendations, close monitoring for cisplatin-related adverse events including renal adverse events (particularly where risk factors of cisplatin-induced renal adverse events may be present), haematological toxicities, and gastrointestinal toxicities [nausea and vomiting] is advised.

For eGFR 45 – 59 mL/min/1.73 m^2, where the cisplatin starting dose in a protocol is:

1. **> 50 mg/m^2** (inclusive of total fractionated doses), clinical consensus is to consider an appropriate alternative treatment protocol especially in patients with either a poor performance status or concomitant nephrotoxic drug exposure. This is supported by the consensus definition of patients with urothelial carcinoma who are unfit for cisplatin-based chemotherapy.[297] However, treatment protocols splitting cisplatin doses a week apart, may be considered as clinically appropriate alternative treatment protocols for selected patients in certain cancers i.e., advanced urothelial cancers.[298,299] In

all other patients, given that higher cumulative cisplatin exposure (> 50 mg/m^2, more frequent administration) increases the risk of renal adverse events,[267,271,280,281] clinical consensus is to reduce the dose by 25 – 50% if proceeding with cisplatin treatment. When determining the extent of dose reduction, factors including treatment intent, patient performance status, and the potential of high cumulative cisplatin exposure should be considered.

2. **≤ 50 mg/m^2** (inclusive of total fractionated doses), clinical consensus is to administer full dose cisplatin in patients with a curative intent, good performance status, and without concomitant nephrotoxic drug exposure. In all other patients, clinical consensus is to either reduce the dose by 25% or consider a clinically appropriate alternative treatment protocol.

For eGFR < 45 mL/min/1.73 m^2, due to the lack of definitive evidence for the impact of dose adjustments on cisplatin pharmacokinetics, toxicity, and therapeutic efficacy, clinical consensus is to avoid cisplatin and use a clinically appropriate alternative treatment protocol.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- For eGFR < 60 mL/min/1.73 m^2, to ensure therapeutic dosing and reduce the risk of a further decline in kidney function from cisplatin-induced renal adverse events, directly mGFR is preferred for initial dosing, especially where either:
    - cisplatin dose > 50 mg/m^2
    - eGFR is unreliable (e.g., extremes of body composition, amputees, paraplegia, conditions of skeletal muscle).

- To minimise the risk of cisplatin-induced renal adverse events, adequate preventative and supportive care measures (as per local institutional policies) are advised for all patients receiving cisplatin. This includes maintaining adequate euvolemia, monitoring urine output through appropriate fluid hydration pre- and post-infusion, and preventing salt-wasting with magnesium and potassium supplementation.[273,280,300] Taking into account the scarcity of evidence, mannitol may be considered to further ameliorate the risk by promoting osmotic diuresis, especially in patients receiving ≥ 100 mg/m^2.[280,300] Monitor kidney function, fluid balance, electrolytes and albumin levels throughout treatment.

- The dose reduction applies to each individual dose within the treatment cycle. For a continuous infusion, the dose reduction refers to the total dose and not the total number of days or duration for the infusion per treatment cycle.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

Table 15 – Cisplatin dose recommendations according to kidney function

<table>
<tr><th colspan="4">INTRAVENOUS CISPLATIN DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th colspan="2">Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td colspan="2">full dose [a]</td><td></td></tr>
<tr><td rowspan="2">45 – 59</td><td><u>When protocol starting dose is ≤ 50 mg/m²</u>

full dose [a,b]

or

reduce by 25% [a,b,c]

or

alternative protocol</td><td><u>When protocol starting dose is > 50 mg/m²</u>

alternative protocol [d]

or

reduce by 25 – 50% [a,b,c]</td><td>In > 50 mg/m² (inclusive of total fractionated doses), consider a clinically appropriate alternative treatment protocol especially in patients with either:
• a poor performance status
• concomitant nephrotoxic drug exposure.
In all other patients, if proceeding with cisplatin, consider a 25 – 50% dose reduction. Extent of dose reduction should take into account:
• intent of treatment
• performance status
• potential total cumulative cisplatin exposure.

In ≤ 50 mg/m² (inclusive of total fractionated doses), consider full dose in patients with:
• <u>curative</u> treatment intent, and
• a good performance status, and
• without concomitant nephrotoxic drug exposure.
In all other patients, consider a 25% dose reduction or a clinically appropriate alternative treatment protocol.

Potential for increased risk of adverse events (i.e., renal toxicities [especially when risk factors present][e], haematological toxicities, nausea and vomiting)</td></tr>
<tr><td>30 – 44</td><td colspan="2" rowspan="3">AVOID</td><td rowspan="3">Not recommended – use a clinically appropriate alternative treatment protocol.</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="3">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="4">[a] Adequate preventative and supportive care measures (as per local institutional policies) are advised for all patients to minimise the risk of cisplatin-induced renal adverse events and include:
– Intravenous hydration, magnesium, and potassium supplementation +/- mannitol
– Monitoring kidney function, urine output, electrolytes, albumin, and fluid balance throughout treatment.
[b] To ensure therapeutic dosing and reduce the risk of a further decline in kidney function from cisplatin-induced renal adverse events, directly measured GFR is preferred for the initial dosing especially where either cisplatin dose > 50 mg/m² or eGFR is unreliable (e.g., extremes of body composition, amputees, paraplegia, conditions of skeletal muscle). Measured GFR refers to a direct measurement of the clearance of exogenous markers such as iohexol, iothalamate, ^{51}Cr-EDTA (radioactive chromium complex with ethylenediaminetetraacetic) or ^{99}Tc-DTPA (TC-diethylenetriaminepentaacetic acid).
[c] The dose reduction applies to each individual dose within the treatment cycle. For a continuous infusion, the dose reduction refers to the total dose and not the total number of days or duration for the infusion per treatment cycle.
[d] Clinically appropriate alternative treatment protocols for selected patients in certain cancers may include protocols that split cisplatin doses a week apart.
[e] Risk factors for developing cisplatin-induced renal adverse events include high peaks of free platinum concentrations (possibly caused by doses > 50 mg/m², more frequent administration, larger cumulative dose, and hypoalbuminaemia), hypertension, concomitant nephrotoxic drug exposure, older age, and poor performance status.</td></tr>
<tr><td colspan="4">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.12 Cyclophosphamide

RECOMMENDATION 4.12.1

We recommend the use of kidney function to inform the initial dosing of intravenous and oral cyclophosphamide in all cancers. Kidney function may inform the monitoring of adverse events.

Cyclophosphamide is a prodrug that is activated in the liver by CYP450 enzymes to produce tautomeric intermediates which go on to form alkylating toxic metabolites (phosphoramide mustard and acrolein) and inactive products.[301-304] The metabolic pathway of cyclophosphamide is saturable, with reduced formation of active metabolites at higher doses (> 1000 mg/m^2) and both increased formation and renal CL of inactive metabolites.[301,305,306] Following repeated administration (e.g., continuous infusion or divided doses over several days), autoinduction of metabolism may compensate for saturation, resulting in shortened $t_{1/2}$ and increased CL of the activation pathway.[305,306]

Cyclophosphamide and its metabolites undergo a variable degree of renal elimination (between 2 – 52% in 24 hours).[301-304,307-311] Factors affecting the renal excretion of cyclophosphamide and its metabolites include dose intensity (increased renal CL of cyclophosphamide in favour of inactive metabolites with higher doses [> 1000 mg/m^2]), variable expression and activity of CYP450 enzymes, and baseline kidney function).[301,302,305,309]

In patients with eGFR < 50 mL/min/1.73 m^2, several pharmacokinetic studies have observed a reduction in CL, prolongation of $t_{1/2}$, and increase in systemic exposure (AUC) of cyclophosphamide and its cytotoxic metabolites compared to patients with normal kidney function.[309,312-316] Changes in the exposure of cytotoxic metabolites are more pronounced and are of clinical significance when eGFR < 30 mL/min/1.73 m^2.[309,313,314] A pharmacokinetic simulation demonstrated that a 90% decline in the renal CL of cyclophosphamide was required to increase systemic exposure of cytotoxic metabolites by 30%.[302]

Several studies in patients with breast cancer receiving cyclophosphamide and doxorubicin treatment have observed a significantly increased risk of grade ≥ 3 non-haematological adverse events with decreased kidney function.[216] Conversely, a study in patients with CLL observed no significant difference in the incidence of grade ≥ 3 non-haematological adverse events with cyclophosphamide treatment in patients with and without kidney dysfunction.[317] Evidence for the effect of kidney

dysfunction on haematological adverse events is also conflicting, with some studies showing no association[216,317] and another showing significantly increased risks of grade ≥ 3 haematological toxicities (i.e., myelosuppression, febrile neutropenia).[318,319] Moreover, whilst one study observed an increased frequency of cyclophosphamide dose reductions in patients with kidney dysfunction (eGFR range 30 – 69 mL/min/1.73 m^2),[317] others have reported no correlation between kidney function and dose adjustments,[216,318] dose delays,[216,317,318] and early treatment cessation.[216,317,318] All aforementioned studies, however, did not include patients with eGFR < 30 mL/min/1.73 m^2. A case report in a patient with eGFR < 15 mL/min/1.73 m^2 requiring KRT demonstrated that full dose (600 mg/m^2) cyclophosphamide was well tolerated, with no dose- or treatment-limiting toxicities.[312]

Haemorrhagic cystitis is a result of the toxic metabolite acrolein accumulating in the urine and damaging the bladder epithelium.[320] The effect of baseline kidney function on the risk of haemorrhagic cystitis is unclear, although adequate urine output to void the bladder of the urotoxic metabolite is necessary to prevent this dose-limiting adverse event.[321,322]

Evidence quality/certainty: ***low****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.12.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous and oral cyclophosphamide in kidney dysfunction.

A small number of studies have partially applied KDIGO CKD categories to guide dose adjustment of cyclophosphamide and the monitoring of adverse events.[216,313,314] Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.12.3

We suggest an initial dose reduction of intravenous and oral cyclophosphamide in kidney dysfunction in non-transplant and non-cellular therapy settings*.

** For stem cell mobilisation, bone marrow transplantation and CAR T-cell therapy conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring cyclophosphamide as part of their treatment. The dose adjustments have not been tailored for these protocols.*

There is a lack of definitive evidence to suggest dose adjustments in eGFR < 60 mL/min/1.73 m^2 will result in a reduced risk of adverse events without compromising therapeutic efficacy. Despite not reaching statistical significance, a small study in patients with post-transplant lymphoproliferative disorders found poorer outcomes (response rates, 5-year survival rates) in patients with eGFR < 50 mL/min/1.73 m^2 (including eGFR < 15 mL/min/1.73 m^2) receiving a 10 – 50% dose reduction in cyclophosphamide compared with patients receiving full dose cyclophosphamide with eGFR ≥ 50 mL/min/1.73 m^2.[323]

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose cyclophosphamide. This is supported by international consensus recommendations in multiple myeloma, where no dose adjustment is required.[198] Despite reduced cyclophosphamide CL and increased AUC when eGFR 30 – 59 mL/min/1.73 m^2,[309,313,314] systemic exposure to active metabolites is only moderately increased and not considered clinically significant.[313-316]

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose cyclophosphamide, especially in patients with a curative intent, with close monitoring for adverse events (i.e., haematological toxicities [myelosuppression, febrile neutropenia], gastrointestinal toxicities [nausea and vomiting]). For patients with a non-curative treatment intent (excluding patients with multiple myeloma) who have a poor performance status and concomitant nephrotoxic drug exposure, consider a 25% dose reduction. Simulation studies suggest a dose reduction of 20 - 30% in patients with an eGFR < 30 mL/min/1.73 m^2 is likely to normalise the AUC of cytotoxic cyclophosphamide metabolites towards ranges present in patients with normal kidney function,[302,309] potentially reducing the risk of severe treatment-related adverse events. In patients with multiple myeloma with the aforementioned risk factors, full dose may be considered as per the international consensus recommendations for multiple myeloma.[198] Real-world data in multiple myeloma patients with eGFR < 30 mL/min/1.73 m^2 (including < 15 mL/min/1.73 m^2) receiving full dose cyclophosphamide show high response rates, with no grade ≥ 3 or dose-limiting toxicities reported.[324,325]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- To reduce the risk of haemorrhagic cystitis from acrolein, adequate urine output and hydration during and post administration of oral and intravenous cyclophosphamide is required.[321,322] Due to the increased risk of haemorrhagic cystitis with higher cyclophosphamide doses (> 1000 mg/m^2), prophylactic administration of mesna and/or hyper-hydration is necessary to decrease the incidence of urothelial toxicity.[321,322] Local preventative hydration and mesna protocols should be followed.

- The dose reduction applies to each individual dose and not to the total number of days or duration of cyclophosphamide per treatment cycle.

- Consider practicality of tablet strength when applying dose reductions to oral cyclophosphamide. Dose adjustments may require rounding to nearest tablet strength to enable delivery of a measurable dose.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

Table 16 – Cyclophosphamide dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS and ORAL CYCLOPHOSPHAMIDE DOSE RECOMMENDATIONS [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose [b]</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>reduce by 25% [b,c,d]
or
full dose [b]</td><td>Consider a 25% dose reduction in patients with:
<u>non-curative</u> intent (excluding multiple myeloma), and
poor performance status, and
concomitant nephrotoxic drug exposure.
In all other patients, consider full dose.

Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression, febrile neutropenia], gastrointestinal toxicities [nausea and vomiting]).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] For stem cell mobilisation, bone marrow transplantation and CAR T-cell therapy conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring cyclophosphamide as part of their treatment. The dose adjustments have not been tailored for these protocols.
[b] Preventative and support care measures (as per local institutional policies) are advised in all patients to reduce the risk of haemorrhagic cystitis and include:
adequate urine output and hydration during and after administration of oral and intravenous cyclophosphamide
for high-dose cyclophosphamide protocols (> 1000 mg/m^2), prophylactic administration of mesna and/or hyper-hydration
[c] The dose reduction applies to each individual dose and not to the total number of days or duration of cyclophosphamide per treatment cycle.
[d] Dose adjustments may require rounding to nearest tablet strength to enable delivery of a measurable dose.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.13 Cytarabine

RECOMMENDATION 4.13.1

We suggest the use of kidney function to inform the initial dosing of intravenous high-dose cytarabine (≥ 1000 mg/m^2) in all cancers. Kidney function may inform the monitoring of adverse events.

We suggest against the use of kidney function to inform the initial dosing of intravenous low-dose cytarabine (< 1000 mg/m^2) in all cancers.

Cytarabine is activated intracellularly to the cytotoxic metabolite aracytidine-5′-triphosphate (Ara-CTP).[326] The transporters involved in intracellular accumulation of Ara-CTP are saturated at high cytarabine plasma concentrations, achieved by doses ≥ 1000 mg/m^2.[327,328] The primary route of elimination of cytarabine is deamination to the inactive (but potentially neurotoxic) metabolite uracil arabinoside (Ara-U), followed by renal excretion, with ~ 80% of the administered dose recovered in urine (~ 10% as unchanged drug and ~ 90% as metabolites, predominantly Ara-U).[326,329,330]

There is a paucity of data on the influence of kidney dysfunction on the pharmacokinetics and clinical outcomes of low-dose cytarabine (< 1000 mg/m^2). In a population pharmacokinetic analysis of low-dose cytarabine (< 1000 mg/m^2) kidney function (eGFR > 47 mL/min/1.73 m^2) did not significantly influence cytarabine pharmacokinetics (CL, V_d).[331] Low-dose cytarabine in patients with eGFR 30 – 59 mL/min/1.73 m^2 was reportedly well tolerated, with no increase in cytarabine-related adverse events compared to patients with normal kidney function.[332,333]

At higher doses (≥ 1000 mg/m^2), the CL of Ara-C and Ara-U appears to be non-linear, suggesting there is saturation of the enzymes involved in the deamination reaction responsible for cytarabine metabolism and elimination.[329,330,334] Despite no influence on the systemic exposure of cytarabine itself, kidney dysfunction (including eGFR < 15 mL/min/1.73 m^2 , with or without KRT) has been associated with significantly increased systemic exposure to the inactive Ara-U metabolite (increased AUC, prolonged $t_{1/2,}$ reduced CL) in high-dose cytarabine (≥ 1000 mg/m^2).[335-339] A case report in a patient with cisplatin-induced kidney dysfunction receiving high-dose cytarabine observed neurotoxicity in association with a 3-fold increase in Ara-U systemic exposure (C_{max}) in comparison to previously reported Ara-U levels in normal kidney function.[337] Numerous other studies have identified

kidney dysfunction (eGFR < 60 mL/min/1.73 m^2) as a significant risk factor for the development of neurotoxicity during high-dose cytarabine treatment.[335,338,339]

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.13.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous high-dose cytarabine (≥ 1000 mg/m^2) in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide the dose adjustment of high-dose cytarabine (≥ 1000 mg/m^2) and the monitoring of adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.13.3

We suggest an initial dose reduction of intravenous high-dose cytarabine (≥ 1000 mg/m^2) in kidney dysfunction in non-transplant settings*.

We suggest against an initial dose reduction of intravenous low-dose cytarabine (< 1000 mg/m^2) in kidney dysfunction in non-transplant settings*.

** For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring this drug as part of their treatment. The dose adjustments have not been tailored for these protocols.*

While there is limited evidence for the impact of dose adjustments on treatment-related adverse events and therapeutic efficacy of high-dose cytarabine (≥ 1000 mg/m^2) in kidney dysfunction, a retrospective review reported that a 30 – 50% dose reduction where eGFR < 60 mL/min/1.73 m^2 significantly reduced the risk of neurotoxicity compared to full dose without adversely affecting response rates.[339] Some studies have pre-emptively dose reduced high-dose cytarabine in patients aged ≥ 60 years (from ≥ 2000 mg/m^2 to 1000 mg/m^2) to reduce the risk of neurotoxicity (often attributed to declining kidney function with ageing) without compromising response rates.[340,341] There is no pharmacokinetic evidence for the impact of dose reductions on cytarabine exposure-response relationships.

For eGFR 30 – 59 mL/min/1.73 m^2, where cytarabine starting dose in a protocol is:

1. **≥ 1000 mg/m^2**, clinical consensus is that a clinically appropriate alternative treatment protocol should be considered in patients with curative intent. If high-dose cytarabine is necessary, consider reducing the dose by 50% with close monitoring for adverse events (i.e., neurotoxicity [CNS neurotoxicity]).

2. **< 1000 mg/m^2**, clinical consensus is to administer full dose. There is currently no evidence in the pharmacokinetics or clinical outcomes to indicate a dose adjustment is necessary in this cohort.[331-333]

For eGFR < 30 mL/min/1.73 m^2, where cytarabine starting dose in a protocol is:

1. **≥ 1000 mg/m^2**, clinical consensus is to avoid high-dose cytarabine and use a clinically appropriate alternative treatment protocol. High-dose cytarabine is not recommended due to the paucity of evidence for the impact of dose adjustments on systemic exposure, adverse events, and therapeutic efficacy. A pharmacokinetic study suggested that a dose reduction > 50% will not saturate the key steps in intracellular Ara-CTP formation, thereby reducing anti-leukemic activity and compromising therapeutic efficacy.[336]

2. **< 1000 mg/m^2**, clinical consensus is to administer full dose. Given the pharmacokinetics of low-dose cytarabine and the limited data in this cohort, it is unlikely that a dose adjustment will reduce the risk of treatment-related adverse events without compromising therapeutic efficacy.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- Ensure dose reductions are not applied to doses from treatment protocols that have already been age-adjusted.[340,341]
- The dose reduction applies to each individual dose and not to the total number of days or duration of cytarabine per treatment cycle

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

Table 17 – Cytarabine dose recommendations according to kidney function

<table>
<tr><th colspan="4">INTRAVENOUS CYTARABINE DOSE RECOMMENDATIONS [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th colspan="2">Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td colspan="2">full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="4"><u>When protocol starting dose is < 1000 mg/m²</u>

full dose</td><td><u>When protocol starting dose is ≥ 1000 mg/m²</u>

alternative protocol

or

reduce by 50% [b,c]</td><td>In ≥ 1000 mg/m², consider a clinically appropriate alternative treatment protocol in patients with a <u>curative</u> treatment intent.
In all other patients, consider a 50% dose reduction.

Increased risk of adverse events (i.e., neurotoxicity [CNS neurotoxicity]).</td></tr>
<tr><td>30 – 44</td><td>In < 1000 mg/m², consider full dose.</td></tr>
<tr><td>15 – 29</td><td rowspan="2"><u>When protocol starting dose is ≥ 1000 mg/m²</u>

AVOID</td><td>In ≥ 1000 mg/m², not recommended – use a clinically appropriate alternative treatment protocol.</td></tr>
<tr><td>< 15 (without KRT)</td><td>In < 1000 mg/m², consider full dose.</td></tr>
<tr><td>KRT</td><td colspan="3">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="4">[a] For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring cytarabine as part of their treatment. The dose adjustments have not been tailored for these protocols.
[b] Avoid further dose reduction if using an age-adjusted dose in a protocol.
[c] The dose reduction applies to each individual dose and not to the total number of days or duration of cytarabine per treatment cycle.</td></tr>
<tr><td colspan="4">Abbreviations: CNS – central nervous system; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.14 Dabrafenib

RECOMMENDATION 4.14.1

We recommend *against* the use of kidney function to inform the initial dosing of oral dabrafenib in all cancers.

The major route of dabrafenib elimination is faecal excretion, with 71% of the administered dose recovered in faeces as either parent drug or metabolite and 23% recovered in urine as metabolites (predominantly carboxy-dabrafenib).[342] Carboxy-dabrafenib is not expected to contribute to the pharmacological activity of dabrafenib.[343] Dabrafenib is highly protein bound (~ 99%),[344] although the impact of hypoalbuminaemia on dabrafenib pharmacokinetics is unclear.

Kidney dysfunction (eGFR range 30 – 59 mL/min/1.73 m^2) does not significantly influence CL or systemic exposure of dabrafenib or its metabolites.[345] A case report in a patient with eGFR < 15 mL/min/1.73 m^2 on KRT observed similar plasma concentrations of dabrafenib to patients with normal kidney function receiving the same dose.[346]

There is insufficient data on the incidence of dabrafenib-related adverse events where eGFR < 30 mL/min/1.73 m^2. A single case report described persistent (but not treatment-limiting) dermatological toxicities with dabrafenib in a patient requiring KRT, despite receiving a 75% reduced dose of dabrafenib resulting in lower plasma concentrations than seen at standard therapeutic dosing.[346] Renal adverse events (i.e., AKI, interstitial nephritis, electrolyte abnormalities) are rarely reported with dabrafenib treatment,[347-350] and do not appear to be influenced by baseline kidney function.

For eGFR 15 – 59 mL/min/1.73 m^2, full dose dabrafenib is recommended.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 18 – Dabrafenib dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL DABRAFENIB DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="4">full dose</td><td rowspan="4"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.15 Dacarbazine

RECOMMENDATION 4.15.1

We suggest the use of kidney function to inform the initial dosing of intravenous dacarbazine in all cancers. Kidney function may inform the monitoring of adverse events.

Dacarbazine is a prodrug which undergoes hepatic biotransformation via CYP450 enzymes to the active metabolite 5-aminoimidazole-4-carboxamide (AIC).[351] Approximately 20 – 50% of the dacarbazine dose is excreted in the urine as unchanged drug and ~ 9 – 30% as AIC by tubular secretion.[352-355]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of dacarbazine. A single case report described a 2.5-fold increase in the $t_{1/2}$ of dacarbazine following administration to a patient with impaired kidney and hepatic function.[355]

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.15.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous dacarbazine in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of dacarbazine and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.15.3

We suggest an initial dose reduction of intravenous dacarbazine in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose dacarbazine. Despite the theoretical risk of altered pharmacokinetics and increased rates of dacarbazine-related adverse events associated with predominately renal excretion, there is an absence of definitive evidence for the impact of dose reductions on adverse events and therapeutic efficacy in kidney dysfunction.

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to consider either a clinically appropriate alternative treatment protocol or to proceed with full dose in patients with curative intent, as limited evidence exists on survival outcomes with dacarbazine dose reduction in kidney dysfunction.[356] Consider a 30% dose reduction if treatment intent is non-curative, as the predominantly renal excretion[352-355] suggests there may be increased adverse events in kidney dysfunction. Close monitoring for dacarbazine-related adverse events (i.e., haematological toxicities [leucopenia, thrombocytopenia], gastrointestinal toxicities [nausea and vomiting]) is advised.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice point

- The dose reduction applies to each individual dose and not to the total number of days of dacarbazine per treatment cycle.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

Table 19 – Dacarbazine dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS DACARBAZINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>alternative protocol
or
full dose
or
reduce by 30% [a]</td><td>Consider either a clinically appropriate alternative treatment protocol or full dose in patients with a curative treatment intent.

Consider a 30% dose reduction in patients with a non-curative treatment intent.

Potential for increased risk of adverse events (haematological toxicities [leucopenia, thrombocytopenia], gastrointestinal toxicities [nausea and vomiting]).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] The dose reduction applies to each individual dose and not to the total number of days of dacarbazine per treatment cycle.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.16 Dactinomycin

RECOMMENDATION 4.16.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous dactinomycin in all cancers. Kidney function may inform the monitoring of adverse events.

Elimination of dactinomycin (or actinomycin D) is thought to be via renal and biliary excretion, with ~ 30% of the dactinomycin dose recovered in the urine and faeces after one week.[357,358]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of dactinomycin. In a population pharmacokinetic analysis of paediatric patients (S_{Cr} range 12 – 90 µmol/L), no association was found between S_{Cr} and dactinomycin CL, or V_d.[359] In a case study of an adult patient with an eGFR 51 mL/min/1.73 m^2, a marked reduction in dactinomycin CL and increased AUC was reported in comparison to patients with normal kidney function.[360] Whilst dactinomycin systemic exposure was not correlated to induction of remission, increased AUC was associated with higher severity of oral mucositis with treatment.[360]

The effect of kidney function on dactinomycin-related adverse events is unclear. The use of full dose dactinomycin was associated with an increased incidence of grade ≥ 3 neutropenia and thrombocytopaenia in a paediatric population with an anephric status or kidney failure in the context of Wilms tumour compared to dose reduced dactinomycin (25 – 75 % dose reduction).[361]

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.16.2

We suggest the use of KDIGO CKD categories to guide monitoring for intravenous dactinomycin-related adverse events in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of dactinomycin and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

*Evidence quality/certainty**: no studies**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.16.3

We suggest *against* an initial dose reduction of intravenous dactinomycin in kidney dysfunction.

For eGFR 15 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose dactinomycin. Given the paucity in data demonstrating a clear relationship between pharmacokinetic changes and adverse events in the adult population with kidney dysfunction, close monitoring for the potential increased incidence and severity of dactinomycin-related adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia], gastrointestinal toxicities [mucositis]) is advised.[360,361]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 20 – Dactinomycin dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS DACTINOMYCIN DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="3">full dose</td><td rowspan="3">Potential for increased risk of adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], gastrointestinal toxicities [mucositis]).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.17 Daunorubicin (including *Liposomal* Daunorubicin)

RECOMMENDATION 4.17.1

We suggest the use of kidney function to inform the initial dosing of intravenous daunorubicin (including *liposomal* daunorubicin) in all cancers. Kidney function may inform the monitoring of adverse events.

Both daunorubicin and *liposomal* daunorubicin are primarily eliminated via hepatic metabolism and biliary excretion, with 4 – 6% of the administered dose excreted in the urine as unchanged daunorubicin and 8 – 12% as the active metabolite daunorubicinol.[362-364] Although *liposomal* daunorubicin has a prolonged $t_{1/2}$, reduced V_d and higher systemic exposure (AUC, C_{max}) compared to conventional daunorubicin,[362,364,365] both formulations follow the same route of elimination.[364,365]

There are no clinically significant differences in the pharmacokinetics of daunorubicin and daunorubicinol (CL, V_d, $t_{1/2}$, AUC, C_{max}) between patients with eGFR 30 – 59 mL/min/1.73 m^2 and eGFR ≥ 60 mL/min/1.73 m^2.[366-369] Reduced daunorubicin CL and increased systemic exposure (AUC), however, were reported in a patient with eGFR < 15 mL/min/1.73 m^2 on KRT compared to historical controls with normal kidney function.[370]

There is a lack of published evidence on the effects of kidney dysfunction on the clinical outcomes of daunorubicin. Although kidney dysfunction is not a definitive risk factor for developing anthracycline dose-dependent cardiotoxicity,[371] potential pharmacokinetic changes in patients with poorer eGFR may increase systemic exposure at standard doses of daunorubicin. Hence, it is advised to avoid exceeding current recommendations on the maximum lifetime cumulative anthracycline dose.[371,372]

Renal adverse events (i.e., nephrotic syndrome, AKI), although rare (incidence < 1%), have been reported with daunorubicin treatment.[373] It is unclear whether baseline kidney dysfunction influences the risk of daunorubicin-related renal adverse events.

Evidence quality/certainty: ***very low;*** *strength of recommendation:* ***conditional.***

RECOMMENDATION 4.17.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of adverse events of intravenous daunorubicin (including *liposomal* daunorubicin) in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of daunorubicin or *liposomal* daunorubicin and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies;*** *strength of recommendation:* ***conditional.***

RECOMMENDATION 4.17.3

We suggest an initial dose reduction of intravenous daunorubicin (including *liposomal* daunorubicin) in kidney dysfunction.

In addition to the following recommendations, close monitoring for adverse events (i.e., haematological toxicities [myelosuppression]) is recommended when eGFR < 60 mL/min/1.73 m^2, given the lack of substantive evidence on the incidence of daunorubicin-related adverse events in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, full dose daunorubicin is suggested due to the lack of significant changes in pharmacokinetics in this cohort compared to eGFR ≥ 60 mL/min/1.73 m^2.[366-369]

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose daunorubicin, given the absence of definitive evidence for the impact of dose reductions on pharmacokinetics, adverse events, and therapeutic efficacy in this setting. In patients with a poor performance status and a non-curative treatment intent, a 25% dose reduction may be considered. A 50% dose reduction of daunorubicin in two patients with eGFR < 15 mL/min/1.73 m^2 requiring KRT was tolerated to a variable degree, with one case experiencing a fatal adverse event,[370] whilst the other experienced no serious haematological toxicities and demonstrated a good clinical response.[374]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- The dose of conventional daunorubicin is different than that of *liposomal* daunorubicin, and the two formulations are not interchangeable. The dose recommendations listed do not account for additional dose adjustments when converting between conventional and *liposomal* daunorubicin.
- The dose reduction applies to each dose and not to the total number of days or duration of daunorubicin per cycle.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

Table 21 – Daunorubicin (and liposomal daunorubicin) dose recommendations according to kidney function

INTRAVENOUS DAUNORUBICIN (including LIPOSOMAL DAUNORUBICIN) DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**full dose**	Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression]).
30 – 44		
15 – 29	**reduce by 25%** [a,b] **or** **full dose**	Consider a 25% dose reduction in patients with: • non-curative treatment intent, *and* • poor performance status. In all other patients, consider full dose. Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression]).
< 15 (without KRT)	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	
KRT		

[a] The dose of conventional daunorubicin is different than that of *liposomal* daunorubicin, and the two formulations are not interchangeable. The dose recommendations listed do not account for additional dose adjustments when converting between conventional and *liposomal* daunorubicin.

[b] The dose reduction applies to each individual dose and not to the total number of days or duration of daunorubicin per treatment cycle.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.18 Docetaxel

RECOMMENDATION 4.18.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous docetaxel in all cancers.

Docetaxel is primarily eliminated via hepatic metabolism and biliary excretion, with ~ 80% of the dose excreted in the faeces (~ 3% as parent drug) and < 5% of the dose excreted in the urine unchanged.[375-378] Docetaxel is extensively bound (> 98%) to plasma proteins (α_1-acid glycoprotein, lipoproteins and albumin), with α_1-acid glycoprotein concentrations inversely correlated to the unbound fraction and CL of docetaxel.[379,380]

The pharmacokinetics of docetaxel are not significantly influenced by kidney function (including eGFR < 15 mL/min/1.73 m^2 and in KRT), with comparable plasma exposure (AUC, C_{max}) and CL in patients with and without kidney dysfunction.[312,381-383]

Docetaxel has not demonstrated a higher incidence of grade ≥ 3 adverse events (i.e., haematological toxicities [febrile neutropenia]) or associated dose adjustments or early treatment cessation directly related to kidney dysfunction.[384-386] No significant differences have been observed in disease control rates and median survival (overall and progression free) between patients with an eGFR 15 – 44 mL/min/1.73 m^2 and an eGFR ≥ 45 mL/min/1.73 m^2 receiving standard docetaxel doses.[387] Renal adverse events (i.e., thrombotic microangiopathy, acute tubular nephrotoxicity, hyponatraemia,), although rare, have been reported with docetaxel treatment, and do not appear to be associated with baseline kidney function.[384,388,389]

For eGFR < 60 mL/min/1.73 m^2, full dose docetaxel is recommended.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 22 – Docetaxel dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS DOCETAXEL DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.19 Doxorubicin

RECOMMENDATION 4.19.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous doxorubicin in all cancers.

Doxorubicin is primarily eliminated via hepatic metabolism and biliary excretion, with ~ 50% excreted in the bile as unchanged doxorubicin and ~ 23% as the cytotoxic metabolite doxorubicinol within 7 days of administration.[390] Renal excretion is a minor route of elimination, with ~ 2 – 6% of the dose excreted in the urine as unchanged doxorubicin and < 2% as doxorubicinol within 48 hours of administration.[390-393]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of doxorubicin. In a population pharmacokinetic analysis, kidney function (eGFR range 40 – 201 mL/min/1.73 m^2) did not significantly influence CL or V_d of doxorubicin.[394] A small pharmacokinetic study, however, observed significantly lower CL and increased AUC of doxorubicin and doxorubicinol in patients with eGFR < 15 mL/min/1.73 m^2 requiring KRT compared to patients with normal kidney function.[395] In breast cancer patients receiving doxorubicin treatment, the incidence of grade ≥ 3 adverse events and associated dose adjustments and treatment cessations was independent of kidney function (eGFR range 22 – 112 mL/min/1.73 m^2).[216] Furthermore, kidney function was not predictive of survival outcomes.[216] Although kidney dysfunction is not a definitive risk factor for developing anthracycline dose-dependent cardiotoxicity,[371] potential pharmacokinetic changes in patients with poorer eGFR may increase systemic exposure at standard doses of doxorubicin. Hence, it is advised to avoid exceeding the maximum lifetime cumulative anthracycline dose.[371,372]

Renal adverse events (i.e., nephrotic syndrome, AKI), although rare, have been reported with doxorubicin treatment.[396] It is unclear whether baseline kidney dysfunction influences the risk of doxorubicin-related renal adverse events.

For eGFR < 60 mL/min/1.73 m^2, full dose doxorubicin is recommended. This is further supported by international consensus recommendations for multiple myeloma.[198]

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **strong***

Table 23 – Doxorubicin dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS DOXORUBICIN DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.20 *Pegylated Liposomal* Doxorubicin

RECOMMENDATION 4.20.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous *pegylated liposomal* doxorubicin in all cancers. Kidney function may inform the monitoring of adverse events.

Pegylated liposomal doxorubicin is a liposomal formulation of doxorubicin delivered to tissues where doxorubicin is released from liposomes and metabolised in the liver.[397] *Pegylated liposomal* doxorubicin displays a prolonged plasma $t_{1/2}$, reduced CL, reduced V_d, and higher systemic exposure (AUC, C_{max}) compared to conventional doxorubicin.[397] Elimination is primarily via hepatic metabolism and biliary excretion, with ~ 5 – 10% of the dose excreted in the urine as unchanged doxorubicin and < 2% excreted as the active metabolite doxorubicinol within 6 days of administration.[398,399]

The pharmacokinetics of *pegylated liposomal* doxorubicin are reported to be independent of kidney function,[400] although data is lacking in patients with eGFR < 30 mL/min/1.73 m^2.

Baseline kidney dysfunction (eGFR 30 – 59 mL/min/1.73 m^2) did not reduce therapeutic efficacy or result in an increased incidence of grade ≥ 3 adverse events with *pegylated liposomal* doxorubicin treatment in patients with multiple myeloma.[182] In a small cohort of gynaecological cancer patients with eGFR 17 – 56 mL/min/1.73 m^2, a low incidence of grade ≥ 3 adverse events was observed with full dose *pegylated liposomal* doxorubicin, although the rate of toxicity-related dose reductions was higher than previous reports in patients with normal kidney function.[401] Therapeutic efficacy was comparable to previous reports in patients with normal kidney function.[401]

Although kidney dysfunction is not a definitive risk factor for developing anthracycline dose-dependent cardiotoxicity,[371] potential pharmacokinetic changes in patients with poorer eGFR may increase systemic exposure at standard doses of *pegylated liposomal* doxorubicin. Hence, it is advised to avoid exceeding current recommendations on the maximum lifetime cumulative anthracycline dose.[371,372] Notably, there were no reports of cardiotoxicity in a small cohort with kidney dysfunction receiving high cumulative doses of *pegylated liposomal* doxorubicin (cumulative dose range 300 – 500 mg/m^2) over 8 – 15 months.[401]

Renal adverse events (i.e., nephrotic syndrome, thrombotic microangiopathy, AKI), although rare (incidence < 1%), have been reported with *pegylated liposomal* doxorubicin.[401-404] It is unclear whether baseline kidney function influences the risk of *pegylated liposomal* doxorubicin-related renal adverse events.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.20.2

We suggest the use of KDIGO CKD categories to guide monitoring for intravenous *pegylated liposomal* doxorubicin-related adverse events in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide monitoring of *pegylated liposomal* doxorubicin-related adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional***.

RECOMMENDATION 4.20.3

We suggest *against* an initial dose reduction of intravenous *pegylated liposomal* doxorubicin in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose *pegylated liposomal* doxorubicin as there is insufficient evidence to indicate a dose reduction will reduce the risk of adverse events without compromising therapeutic efficacy. In a small cohort of patients with kidney dysfunction (eGFR 36 – 56 mL/min/1.73 m^2), full dose *pegylated liposomal* doxorubicin appeared well tolerated with a low incidence of grade ≥ 3 adverse events and subsequent dose reductions.[401] Additionally, kidney dysfunction has not been associated with changes in the pharmacokinetics of *pegylated liposomal* doxorubicin.[400]

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose with close monitoring for *pegylated liposomal* doxorubicin-related adverse events (i.e., gastrointestinal toxicities [mucositis], dermatological toxicities [palmar-plantar erythrodysesthesia], haematological toxicities [neutropenia, anaemia]) given the insufficient pharmacokinetic and toxicity data in this cohort. In a small cohort of patients with eGFR 17 – 29 mL/min/1.73 m^2 receiving full dose *pegylated liposomal* doxorubicin, a low incidence of grade ≥ 3 adverse events were observed, although dose reductions were more frequently required in patients initiated on full dose versus a reduced dose (12.5 – 25% initial dose reduction).[401]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 24 – Pegylated liposomal doxorubicin dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS PEGYLATED LIPOSOMAL DOXORUBICIN
DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR
(mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>full dose</td><td>Potential for increased risk of adverse events (i.e., gastrointestinal toxicities [mucositis], dermatological toxicities [palmar-plantar erythrodysesthesia], haematological toxicities [neutropenia, anaemia]).</td></tr>
<tr><td>< 15
(without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.21 Durvalumab

RECOMMENDATION 4.21.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous durvalumab in all cancers.

Durvalumab has a large molecular weight (~ 149 kDa) and is therefore unlikely to undergo glomerular filtration or urinary excretion. Protein catabolism via the reticuloendothelial system or target-mediated disposition are the primary mechanisms of durvalumab elimination.[405]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of durvalumab treatment. In a population pharmacokinetic analysis, declining kidney function was associated with reduced durvalumab CL, although this effect was not deemed clinically significant and did not include patients with eGFR < 27 mL/min/1.73 m^2.[406]

Immune-related renal adverse events (i.e., AKI involving acute interstitial nephritis or glomerular disease), although rare (incidence < 1%), have been reported with durvalumab treatment.[407-412] The impact of baseline kidney dysfunction on the risk of immune-related renal adverse events with durvalumab is unclear, with some studies reporting no association[409,411] and another observing an increased risk of immune-checkpoint inhibitor-associated AKI with declining kidney function.[407]

A higher risk of graft rejection has been observed in kidney transplant patients (especially allografts) receiving immune checkpoint inhibitors,[413-415] however, there is currently no data regarding the use of durvalumab in kidney transplant patients. The likelihood of graft rejection versus the possible therapeutic benefits of durvalumab needs to be carefully considered in such cases.[416]

For eGFR < 60 mL/min/1.73 m^2, full dose durvalumab is suggested.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice point

- In accordance with international guidelines,[416] measuring baseline kidney function, electrolyte levels and urinalysis are advised before commencement and as clinically indicated throughout durvalumab treatment to monitor for developing immune-related renal adverse events. This is particularly pertinent in patients with additional risk factors for developing immune-related AKI (i.e., concomitant nephrotoxic drug exposure, combination immune checkpoint inhibitor therapy, dehydration).[407,409,411]

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

Table 25 – Durvalumab dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS DURVALUMAB DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose [a]</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">[a] Measurement of baseline kidney function, electrolyte levels and urinalysis are advised before commencement and as clinically indicated throughout durvalumab treatment to monitor for developing immune-related renal adverse events. This is particularly pertinent in patients with additional risk factors for developing immune-related AKI (i.e., concomitant nephrotoxic drug exposure, combination immune checkpoint inhibitor therapy, dehydration).</td></tr>
<tr><td colspan="3">Abbreviation: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.22 Epirubicin

RECOMMENDATION 4.22.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous epirubicin in all cancers.

Epirubicin is primarily eliminated by hepatic metabolism, with < 15% of the administered dose excreted in urine in 48 hours as unchanged drug or metabolites.[391,417-419] Epirubicinol is the only known cytotoxic metabolite of epirubicin, however it is unlikely to reach plasma concentrations required to cause toxicity.[418]

Small studies have observed no significant difference in the pharmacokinetics (CL, AUC, V_d) of either epirubicin or epirubicinol in patients with and without kidney dysfunction,[420-422] although data is lacking in patients with eGFR < 30 mL/min/1.73 m^2.

There is a paucity of data on the incidence of epirubicin-related adverse events in patients with kidney dysfunction. Two case studies in patients receiving full dose epirubicin whilst on KRT did not report any grade ≥ 3 epirubicin-related adverse events,[423,424] with one case remaining relapse-free at 5 years.[423] Although kidney dysfunction is not a definitive risk factor for developing anthracycline dose-dependent cardiotoxicity, potential pharmacokinetic changes in patients with poorer eGFR may increase systemic exposure at standard doses of epirubicin.[371] Hence, it is advised to avoid exceeding the maximum lifetime cumulative anthracycline dose.[371,372]

For eGFR 15 – 59 mL/min/1.73 m^2, full dose epirubicin is recommended.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **very low**; strength of recommendation: **strong**.*

Table 26 – Epirubicin dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS EPIRUBICIN DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="4">full dose</td><td rowspan="4"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.23 Etoposide (and Etoposide *Phosphate*)

RECOMMENDATION 4.23.1

We recommend the use of kidney function to inform the initial dosing of oral and intravenous etoposide (including etoposide *phosphate*) in all cancers. Kidney function may inform the monitoring of adverse events.

Etoposide is metabolised in the liver primarily via CYP450 enzymes and undergoes both biliary and renal excretion.[425] Approximately 40% of the administered dose is excreted in the urine as unchanged drug and ~ 10% as the inactive metabolite etoposide glucuronide.[426-429] Etoposide is highly protein bound (~ 94%), mostly to albumin, with the unbound etoposide fraction correlating to free etoposide AUC and severity of haematological toxicities.[430]

The pharmacokinetics of etoposide are correlated to kidney function, with significantly reduced etoposide CL, prolonged elimination $t_{1/2}$, and increased total-drug and free-drug exposure (AUC) observed with declining kidney function (including in eGFR < 15 mL/min/1.73 m^2).[331,426,429-433] The percentage of dose excreted in the urine as etoposide or etoposide glucuronide is also reduced with kidney dysfunction,[426,429] which may result in increased systemic exposure to etoposide.

An increased incidence and severity of etoposide-related haematological toxicities (i.e., leucopenia, neutropenia, thrombocytopenia) has been observed with decreasing kidney function.[430,433]

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong***.

RECOMMENDATION 4.23.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral and intravenous etoposide (including etoposide *phosphate*) in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of etoposide and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.23.3

We recommend an initial dose reduction of oral and intravenous etoposide (including etoposide *phosphate*) in kidney dysfunction in non-transplant settings*.

* *For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring this drug as part of their treatment. The dose adjustments have not been tailored for these protocols.*

In addition to the following recommendations, close monitoring for haematological adverse events is advised where eGFR < 60 mL/min/1.73 m^2, given the evidence of higher etoposide systemic exposure[331,426,429-433] and increased incidence and severity of haematological toxicities (i.e., leucopenia, neutropenia, thrombocytopenia) in kidney dysfunction.[430,433]

For eGFR 45 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose etoposide given the absence of definitive evidence for the impact of dose reductions on etoposide pharmacokinetics, therapeutic efficacy, and incidence of toxicities in this setting.

For eGFR 30 – 44 mL/min/1.73 m^2, clinical consensus is to administer full dose etoposide due to the absence of definitive evidence for the impact of dose adjustments on toxicity and therapeutic efficacy. Given the increased risk and severity of haematological toxicities in this cohort,[430,433] a dose reduction of 25% may be considered to reduce etoposide systemic exposure where either treatment intent is non-curative, or the patient has a poor performance status.

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to reduce the dose by 25%, which is likely to reduce etoposide systemic exposure and the associated risk of haematological toxicities to a level comparable to patients with normal kidney function receiving full dose.[430,433] The impact of dose reductions on survival outcomes in this cohort has not been investigated.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- Intravenous etoposide *phosphate* 113.6 mg (pro-drug of etoposide) is equivalent to intravenous etoposide (base) 100 mg.[425] The dose recommendations listed do not account for additional dose adjustments when converting between intravenous etoposide (base) and etoposide *phosphate*.
- The bioavailability of oral etoposide is ~ 60% of the intravenous route, however interpatient variability is high, and bioavailability is dependent on dose.[4] The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral etoposide.
- The dose reduction applies to each individual dose and not to the total number of days or duration of etoposide per treatment cycle.
- Dose adjustments may require rounding to nearest capsule strength to enable delivery of a measurable dose.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

Table 27 – Etoposide (and etoposide phosphate) dose recommendations according to kidney function

ORAL and INTRAVENOUS ETOPOSIDE (including ETOPOSIDE PHOSPHATE) DOSE RECOMMENDATIONS [a]		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**full dose**	Increased risk of adverse events (i.e., haematological toxicities [leucopenia, neutropenia, thrombocytopenia]).
30 – 44	**reduce by 25%** [b,c,d,e] **or** **full dose**	Consider a 25% dose reduction in patients with *either*: • non-curative intent of treatment • a poor performance status. In all other patients, consider full dose. Increased risk of adverse events (i.e., haematological toxicities [leucopenia, neutropenia, thrombocytopenia]).
15 – 29	**reduce by 25%** [b,c,d,e]	Increased risk of adverse events (i.e., haematological toxicities [leucopenia, neutropenia, thrombocytopenia]).
< 15 (without KRT)	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	
KRT		

[a] For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring this drug as part of their treatment. The dose adjustments have not been tailored for these protocols.
[b] The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral etoposide. The bioavailability of oral etoposide is ~ 60%, however interpatient variability is high, and bioavailability is dependent on dose.
[c] Etoposide phosphate 113.6 mg (pro-drug of etoposide) is equivalent to etoposide 100 mg. The dose recommendations listed do not account for additional dose adjustments when converting between etoposide and etoposide phosphate.
[d] The dose reduction applies to each individual dose and not to the total number of days or duration of etoposide per treatment cycle.
[e] Dose adjustments may require rounding to nearest capsule strength to enable delivery of a measurable dose.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.24 Everolimus

RECOMMENDATION 4.24.1

We suggest *against* the use of kidney function to inform the initial dosing of oral everolimus in all cancers. Kidney function may inform the monitoring of adverse events.

Everolimus is eliminated primarily by hepatic metabolism via CYP450 enzymes,[434] with 80% of everolimus excreted in bile and 5% excreted in urine as metabolites.[435]

Although there is limited published data on the effect of kidney dysfunction on the pharmacokinetics of everolimus in cancer patients, kidney dysfunction is not expected to influence systemic exposure. A case series of two patients with metastatic renal cell carcinoma (RCC) and an eGFR < 30 mL/min/1.73 m^2 observed similar everolimus plasma concentrations to patients with normal kidney function, with no influence of KRT on plasma concentrations.[436] In a population pharmacokinetic analysis in non-cancer patients (organ transplantation), kidney dysfunction (eGFR range 26 – 59 mL/min/1.73 m^2 and S_{Cr} range 55 – 380 µmol/L) did not significantly influence the V_d[437] and CL[437,438] of everolimus.

Despite occasional reports of everolimus-related dose-limiting and treatment-limiting toxicities in patients with eGFR < 15 mL/min/1.73 m^2,[436,439] full dose everolimus appears to be generally well tolerated in patients with an eGFR < 60 mL/min/1.73 m^2.[439-443] These studies report a low incidence of grade ⩾ 3 adverse events (i.e., mucositis, pneumonitis, haematological toxicities, skin toxicities), associated dose reductions and early treatment cessation.[439-443] Limited data suggests that the therapeutic efficacy (response rate, progression free survival) of everolimus in patients with RCC is not compromised by pre-existing kidney dysfunction.[439]

Renal adverse events (i.e., proteinuria, AKI, acute tubular necrosis) are commonly observed with everolimus treatment in the setting of RCC,[444-446] with the incidence increasing as baseline kidney function declines.[444,446] Case reports have also described everolimus-related renal adverse events in other cancers, including breast cancer, although the risk is not associated with baseline kidney function.[447-449]

For eGFR 15 – 59 mL/min/1.73 m^2, full dose everolimus is suggested with close monitoring for the development of renal adverse events, particularly in patients with additional risk factors (i.e., RCC, concomitant nephrotoxic drug exposure, previous

nephrectomy, kidney dysfunction during previous vascular endothelial growth factor receptor–tyrosine kinase inhibitor [VEGFR–TKI] treatment[444,446,447]).

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- Consider TDM for patients with an eGFR < 60 mL/min/1.73 m^2 where there is concern for the development of severe toxicities. Everolimus has a narrow therapeutic window and high interindividual pharmacokinetic variability which makes it an ideal candidate for TDM-guided dosing.[450]
  - For cancer treatment, a trough concentration target < 20 ng/mL has been proposed to reduce the risk of toxicity,[451-455] and a target concentration > 12 ng/mL proposed as a threshold to optimise progression-free survival.[451,456] Before TDM can be routinely implemented for everolimus dosing in the cancer setting, further research is required to define and validate the exposure-response relationships in renal, breast, and neuroendocrine cancers.[450]
  - In cases where patients are also receiving everolimus as an immunosuppressant post organ transplantation, multidisciplinary input from a specialist transplant team is advised to inform TDM-guided dosing.[457]

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 28 – Everolimus dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL EVEROLIMUS DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="3">full dose [a]</td><td rowspan="3">Increased risk of renal adverse events (i.e., proteinuria, AKI, acute tubular necrosis), especially in patients with either:
RCC
concomitant nephrotoxic drug exposure
previous nephrectomy
kidney dysfunction during prior VEGFR–TKI treatment.</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] Therapeutic drug monitoring may be an option where there is concern for the development of severe toxicities.</td></tr>
<tr><td colspan="3">Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy; RCC, renal cell carcinoma; VEGFR-TKI, vascular endothelial growth factor receptor–tyrosine kinase inhibitor.</td></tr>
</table>

4.25 Fludarabine

RECOMMENDATION 4.25.1

We recommend the use of kidney function to inform the initial dosing of oral and intravenous fludarabine in all cancers. Kidney function may inform the monitoring of adverse events.

Fludarabine is a prodrug that is dephosphorylated in plasma to the primary metabolite 9-β-D-arabinofuranosyl-2-fluoroadenine (F-ara-A), and further converted intracellularly to its active metabolite 9-β-D-arabinofuranosyl-2-fluoroadenine triphosphate (F-ara-ATP).[458,459] Approximately 40 – 60% of the administered dose of fludarabine is excreted in urine as F-ara-A within 24 hours.[458,459]

Pharmacokinetic studies have demonstrated a linear relationship between kidney function and CL of both fludarabine and F-ara-A, with reduced CL and increased systemic exposure (AUC) as eGFR declines, although data where eGFR < 25 mL/min/1.73 m^2 is limited.[460-463]

An increased incidence and severity of potentially fatal fludarabine-related adverse events (i.e., haematological toxicities [myelosuppression, lymphopenia], neurotoxicity)[464-466] and poorer survival outcomes,[463,466] have been reported in patients with kidney dysfunction, including those undergoing conditioning regimens for bone marrow transplantation. There is a paucity of data on clinical outcomes of fludarabine in patients with eGFR < 25 mL/min/1.73 m^2.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.25.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral and intravenous fludarabine in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of fludarabine and the monitoring of adverse events. Clinical

consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.25.3

We recommend an initial dose reduction of oral and intravenous fludarabine in kidney dysfunction in non-transplant and non-cellular therapy settings*.

**For bone marrow transplantation or CAR T-cell conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring fludarabine as part of their treatment. The dose adjustments have not been tailored for these protocols.*

In addition to the following recommendations, close monitoring for fludarabine-related adverse events (i.e., haematological toxicities [myelosuppression, lymphopenia], neurotoxicity) is advised given the increased incidence and severity of potentially fatal adverse events where eGFR < 60 mL/min/1.73 m^2.[464-466]

For eGFR 30 – 59 mL/min/1.73 m^2, where fludarabine is being used in:

1. **Chronic lymphocytic leukemia (CLL),** a dose reduction of 20% is recommended in patients with mutated gene sequence of immunoglobulin heavy-chain variable region (*IGHV*), without a 17p deletion or *TP53* gene mutation, and with a good performance status, as fludarabine treatment is favourable in these patients.[467] A dose reduction of 20% in patients with eGFR 30 – 59 mL/min/1.73 m^2 reduces systemic exposure of F-ara-A and the incidence and severity of adverse events to levels comparable to patients with normal kidney function receiving full dose fludarabine.[462] In all other patients, consider a clinically appropriate alternative treatment protocol.

2. **Acute myeloid leukaemia (AML)**, due to a lack of substantial evidence, clinical consensus is to consider a clinically appropriate alternative treatment protocol especially where the patient has either a poor performance status or concomitant nephrotoxic drug exposure (i.e., cytarabine). In all other patients, consider reducing the dose by 50%. Case reports suggest that patients with kidney dysfunction are more susceptible to severe (and potentially fatal) treatment-related neurotoxicity with full dose fludarabine and cytarabine, due to increased

exposure to fludarabine and F-ara-ATP and their synergistic effects with cytarabine.[464] Given therapeutic systemic exposure of F-ara-ATP was maintained with a 50% dose reduction in combination with cytarabine-containing AML protocols, a small pharmacokinetic study proposes a dose reduction of 50% in patients with kidney dysfunction would maintain therapeutic efficacy.[468] The impact of fludarabine dose reductions on systemic exposure and survival outcomes in AML patients with kidney dysfunction is unclear.

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to avoid using fludarabine and to consider a clinically appropriate alternative treatment protocol. This is justified by the significant pharmacokinetic changes (reduced CL and increased AUC of fludarabine and F-ara-A),[459,462,463] increases in incidence and severity of potentially fatal fludarabine-related adverse events,[460,461,464] and an absence of evidence to support an appropriate dose reduction at this level of kidney dysfunction without compromising therapeutic efficacy.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- The bioavailability of oral fludarabine is approximately 55% of the intravenous route.[467] The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral fludarabine.
- The dose reduction applies to each individual dose and not to the total number of days or duration of fludarabine per treatment cycle.
- Dose adjustments may require rounding to the nearest tablet strength to enable delivery of a measurable dose.

*Evidence quality/certainty: **moderate**; strength of recommendation: **strong**.*

Table 29 – Fludarabine dosing recommendations according to kidney function

<table>
<tr><th colspan="4">ORAL and INTRAVENOUS FLUDARABINE DOSING RECOMMENDATION [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th colspan="2">Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td colspan="2">full dose</td><td></td></tr>
<tr><td>45 – 59</td><td><u>When dosing in CLL</u>

reduce by 20% [b,c,d]

or

alternative protocol</td><td><u>When dosing in AML</u>

alternative protocol

or

reduce by 50% [b,c,d]</td><td>In CLL, consider a 20% dose reduction in patients with:
• mutated IGHV, and
• no 17p deletion or TP53 gene mutation, and
• good performance status.
In all other patients, consider a clinically appropriate alternative treatment protocol.

In AML, consider a clinically appropriate alternative treatment protocol, especially in patients with either:
• poor performance status
• concomitant nephrotoxic drug exposure (i.e., cytarabine).
In all other patients, consider a 50% dose reduction.

Increased risk of adverse events (i.e., haematological toxicities [myelosuppression, lymphopenia], neurotoxicity).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td colspan="2" rowspan="2">AVOID</td><td rowspan="2">Not recommended - use a clinically appropriate alternative treatment protocol.</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="3">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="4">[a] For bone marrow transplantation or CAR T-cell conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring this fludarabine as part of their treatment. The dose adjustments have not been tailored for these protocols.
[b] The bioavailability of oral fludarabine is approximately 55% of the intravenous route. The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral fludarabine
[c] Dose adjustments may require rounding to the nearest tablet strength to enable delivery of a measurable dose.
[d] The dose reduction applies to each individual dose and not to the total number of days or duration of fludarabine per treatment cycle.</td></tr>
<tr><td colspan="4">Abbreviations: AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; IGHV, immunoglobulin heavy-chain variable region; KRT, kidney replacement therapy.</td></tr>
</table>

4.26 Fluorouracil

RECOMMENDATION 4.26.1

We suggest the use of kidney function to inform the initial dosing of intravenous fluorouracil in all cancers. Kidney function may inform the monitoring of adverse events.

Fluorouracil (also known as 5-fluorouracil [5-FU]) is primarily eliminated via hepatic enzymatic catabolism (mainly by dihydropyrimidine dehydrogenase [DPD]) to inactive metabolites.[469-471] Approximately 80% of the administered dose is excreted in urine, mostly as inactive metabolites and < 11% as unchanged fluorouracil.[469-471] As DPD is the first and rate-limiting step in the catabolic pathway of fluorouracil, polymorphisms in the gene encoding DPD (*DPYD*) may lead to reduced enzyme activity, resulting in severe (sometimes fatal) toxicity due to the inability to effectively clear fluorouracil.[206]

The pharmacokinetics of fluorouracil (AUC, V_d, $t_{1/2}$, CL) are not significantly influenced by kidney function (including eGFR < 15 mL/min/1.73 m^2 and KRT).[472-474]

A higher incidence of grade ≥ 3 fluorouracil-related adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis, diarrhoea], cardiotoxicity) and subsequent dose reductions, treatment interruptions and early cessation has been observed in patients with kidney dysfunction (eGFR < 15 – 59 mL/min/1.73 m^2) compared to those with normal kidney function.[209,319,475-479]

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.26.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous fluorouracil in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide the dose adjustment of fluorouracil and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.26.3

We suggest an initial dose reduction of intravenous fluorouracil in kidney dysfunction.

In addition to the following recommendations, close monitoring for adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis, diarrhoea], cardiotoxicity) is advised where eGFR < 60 mL/min/1.73 m^2, given the increased incidence of grade ≥ 3 adverse events and associated dose reductions, treatment interruptions and early cessation in kidney dysfunction.[209,319,475-479]

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose fluorouracil as there is limited evidence that a dose reduction will reduce the risk of adverse events or dose interruptions without compromising therapeutic efficacy.[209,478,480] In several studies, dose reductions of 30 – 65% in solid tumour patients compromised response rates[480] and progression free survival.[209] A 25% dose reduction may be appropriate for patients with either a non-curative treatment intent, poor performance status, or concomitant nephrotoxic drug exposure.[475]

For eGFR 15 – 29 mL/min/1.73 m^2, due to the lack of evidence on the impact of dose reductions on survival outcomes, clinical consensus is to administer full dose fluorouracil in patients with a curative treatment intent who have a good performance status and are not exposed to concomitant nephrotoxic agents. In all other situations, consider a clinically appropriate alternative treatment protocol or a 25% dose reduction to reduce the risk of adverse events and treatment interruptions or early cessation.[475,480]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- *DPYD* genotype testing is advised by regulatory bodies prior to initiating therapy with fluoropyrimidines, as reduced activity of DPD profoundly increases the risk for severe or even fatal toxicities with fluoropyrimidine drugs.[206,220] Doses should be adjusted according to predicted DPD enzyme activity and kidney function.[206,220]

- TDM, where available, may provide an additional option for dosing patients with colorectal or head and neck cancers and eGFR < 60 mL/min/1.73 m^2, where there is concern for the development of severe toxicities.[481-483]

- The dose reduction applies to each individual dose within the treatment cycle, including both bolus and continuous/intermittent infusions. For a continuous infusion, the dose reduction refers to the total dose and not the total number of days or duration for the infusion per treatment cycle.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

Table 30 – Fluorouracil dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS FLUOROURACIL DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose [a]</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="2">reduce by 25% [a,b,c]
or
full dose [a,b]</td><td rowspan="2">Consider a 25% dose reduction in patients with either:
• non-curative treatment intent
• a poor performance status
• concomitant nephrotoxic drug exposure.
In all other patients, consider full dose.

Increased risk of adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis, diarrhoea], cardiotoxicity)</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>alternative protocol
or
reduce by 25% [a,b,c]
or
full dose [a,b]</td><td>Consider a clinically appropriate alternative treatment protocol or a 25% dose reduction in patients with either:
• non-curative treatment intent
• a poor performance status
• concomitant nephrotoxic drug exposure.
In all other patients, consider full dose.

Increased risk of adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis, diarrhoea], cardiotoxicity).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] DPYD genotype testing is advised by regulatory bodies prior to initiating therapy with fluoropyrimidines, as reduced activity of DPD profoundly increases the risk for severe or even fatal toxicities with fluoropyrimidine drugs. Doses should be adjusted according to predicted DPD enzyme activity and kidney function.
[b] Therapeutic drug monitoring, where available, may provide an additional option for dosing patients with colorectal or head and neck cancers and eGFR < 60 mL/min/1.73 m^2, where there is concern for the development of severe toxicities.
[c] The dose reduction applies to each individual dose within the treatment cycle, including both bolus and continuous/intermittent infusions. For a continuous infusion, the dose reduction refers to the total dose and not the total number of days or duration for the infusion per treatment cycle.</td></tr>
<tr><td colspan="3">Abbreviations: DPYD, dihydropyrimidine dehydrogenase gene; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.27 Gemcitabine

RECOMMENDATION 4.27.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous gemcitabine in all cancers. Kidney function may inform the monitoring of adverse events.

Gemcitabine is a prodrug requiring intracellular phosphorylation to the active gemcitabine diphosphate (dFdCDP) and triphosphate (dFdCTP) metabolites for its cytotoxic effects.[484] Only a small amount of gemcitabine is phosphorylated to these active metabolites, with ~ 75% deaminated in plasma and the liver to the inactive 2, 2′-difluorodeoxyuridine (dFdU) metabolite.[485] Intracellularly, dFdU can also be phosphorylated to diphosphate (dFdUDP) and triphosphate (dFdUTP) metabolites, which at low concentrations, have negligible cytotoxic effects.[486] Gemcitabine itself is excreted only to a limited extent by the kidneys (< 10% recovered unchanged in the urine), whilst the primary dFdU metabolite is excreted almost completely by the kidneys (92 – 98% unchanged in the urine).[484,485]

The pharmacokinetics of gemcitabine itself are not reported to change with kidney dysfunction, however, reduced kidney function has been correlated with significantly decreased CL, prolonged terminal $t_{1/2}$ and increased AUC of the dFdU metabolite.[485,487-494] The effect of kidney dysfunction on intracellular concentrations of gemcitabine's active metabolites, dFdCDP and dFdCTP, are unclear. Given that intracellular conversion of dFdCTP is saturable at therapeutic plasma concentrations of gemcitabine,[485,495] dFdCTP concentrations are unlikely to increase in kidney dysfunction. A single case report, however, observed a 4-fold increase in intracellular dFdCTP concentration in a patient with eGFR < 15 mL/min/1.73 m^2 on KRT receiving gemcitabine, compared to historical controls in patients with normal kidney function.[490]

There is limited published evidence regarding the effects of kidney dysfunction on the clinical outcomes of gemcitabine treatment. Baseline kidney dysfunction (eGFR 15 – 59 mL/min/1.73 m^2) was not associated with an increased risk of adverse events in patients receiving gemcitabine 900 mg/m^2.[496] One small study observed a similar incidence of gemcitabine-related dose-limiting haematological toxicities in patients with elevated S_{Cr} (range 147 – 283 µmol/L) and normal kidney function receiving the same dose, however only patients with elevated S_{Cr} experienced dose-limiting dermatological toxicities [skin rash] despite initiation at lower doses.[494] Case reports where full dose (1000 mg/m^2) gemcitabine was administered in patients with eGFR < 15 mL/min/1.73 m^2 in KRT have demonstrated a manageable toxicity

profile (grade ≤ 3 myelosuppression, hepatic transaminase elevations),[489,491] with grade 4 thrombocytopenia and subsequent dose reduction described in only one case.[490] In this case, it was hypothesised that reduced dFdU elimination in kidney dysfunction could result in higher intracellular concentrations of dFdUDP and dFdUTP metabolites, possibly increasing the risk for gemcitabine-related toxicity.[490]

The most common (incidence between 0.02 to 2.20%) .and severe gemcitabine-related renal adverse event is haemolytic uraemic syndrome (HUS) involving AKI with associated haemolytic anaemia, thrombocytopenia, proteinuria, and hypertension.[497-499] It is unclear whether there is an association between baseline kidney function and the incidence of HUS with gemcitabine treatment.

Evidence quality/certainty: ***low****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.27.2

We suggest the use of KDIGO CKD categories to guide monitoring for intravenous gemcitabine-related adverse events in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of gemcitabine and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.27.3

We suggest *against* an initial dose reduction of intravenous gemcitabine in kidney dysfunction.

For eGFR 15 – 59 mL/min/1.73 m^2, clinical consensus is that full dose gemcitabine is appropriate given the absence of definitive evidence for the impact of dose reductions on survival outcomes and response rates in this setting. Among patients with urothelial carcinoma with an eGFR < 60 mL/min/1.73 m^2, overall survival was significantly reduced in patients treated with a reduced dose of gemcitabine and cisplatin compared to those treated with standard-dosing.[295] Additionally, dose reductions have not demonstrated a decreased risk of gemcitabine-related adverse events.[490,494] Given the toxicity implications of dFdU accumulation in kidney dysfunction are unclear, close monitoring for adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia, anaemia] hepatic transaminase elevations, dermatological toxicities [skin rash]) is advised.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 31 – Gemcitabine dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS GEMCITABINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="3">full dose</td><td rowspan="3">Potential for increased risk of adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia, anaemia] hepatic transaminase elevations, dermatological toxicities [skin rash]).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.28 Idarubicin

RECOMMENDATION 4.28.1

We suggest the use of kidney function to inform the initial dosing of oral and intravenous idarubicin in all cancers. Kidney function may inform the monitoring of adverse events.

Idarubicin is extensively metabolised in the liver to the active metabolite idarubicinol.[500-502] Idarubicin is excreted in faeces (~ 17%) and in the urine as either unchanged drug (~ 2 – 7%) or idarubicinol (~ 9 – 13%).[500-503] Both idarubicin and idarubicinol are highly protein bound (97% and 94%, respectively),[501] although the effect of kidney dysfunction on the unbound fraction and systemic exposure of idarubicin is unknown.

There is limited published data regarding the effects of kidney dysfunction on the pharmacokinetics of idarubicin. In a pharmacokinetic study, although idarubicin V_d and AUC were independent of kidney function, idarubicin CL was found to be 30% lower in patients with kidney dysfunction (eGFR range 25 – 59 mL/min/1.73 m^2) compared to normal kidney function.[504] Idarubicinol terminal $t_{1/2}$ was also significantly increased in kidney dysfunction and a non-significant trend for increased idarubicinol AUC was observed.[504]

Idarubicin has not demonstrated a higher incidence of adverse events (i.e., haematological toxicities [myelosuppression]) directly related to kidney dysfunction,[504] although data in patients with eGFR < 30 mL/min/1.73 m^2 is limited to case reports.[374,505] Although kidney dysfunction is not a definitive risk factor for anthracycline dose-dependent cardiotoxicity,[371] potential pharmacokinetic changes in patients with poorer eGFR may increase systemic exposure at standard doses of idarubicin. It is therefore advised to avoid exceeding current recommendations on the maximum lifetime cumulative anthracycline dose.[371,372]

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.28.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral and intravenous idarubicin in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of idarubicin and the monitoring of adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.28.3

We suggest an initial dose reduction of oral and intravenous idarubicin in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose idarubicin given the absence of definitive evidence for the impact of dose adjustment on pharmacokinetics, adverse events, and therapeutic efficacy in this cohort.

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose idarubicin in patients with a curative intent, a good performance status and without concomitant nephrotoxic drug exposure. For all other patients, consider a dose reduction of 30% to reduce the risk of severe idarubicin-related adverse events. Given reduced idarubicin CL and increased idarubicinol $t_{1/2}$ have been correlated to an increased severity of idarubicin-related haematological toxicities,[506,507] pharmacokinetic changes in kidney dysfunction[504] may result in increased severity of idarubicin-related adverse events. Case reports have demonstrated no significant increases in toxicity or changes in therapeutic efficacy when idarubicin dose reductions of 25 – 35% have been administered in eGFR < 15 mL/min/1.73 m^2,[374,505] with one patient tolerating up-titration to full dose idarubicin.[505] There is insufficient data, however, on the impact of dose reductions on pharmacokinetics and therapeutic efficacy. Close monitoring for adverse events (i.e., haematological toxicities [myelosuppression]) is advised, especially if administering full dose.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- The bioavailability of oral idarubicin is variable and is reported to be ~ 30% of the intravenous route.[504] The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral idarubicin.
- The dose reduction applies to each individual dose and not to the total number of days or duration of idarubicin per treatment cycle.
- Dose adjustments may require rounding to the nearest capsule strength to enable delivery of a measurable dose.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

Table 32 – Idarubicin dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL and INTRAVENOUS IDARUBICIN DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>full dose
or
reduce by 30% [a,b,c]</td><td>Consider full dose in patients with:
• <u>curative</u> treatment intent, and
• good performance status, and
• no concomitant nephrotoxic drug exposure.
In all other patients, consider a 30% dose reduction.

Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression]).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] The dose reduction applies to each individual dose and not to the total number of days or duration of idarubicin per treatment cycle.
[b] The dose adjustments may require rounding to the nearest capsule strength to enable delivery of a measurable oral dose.
[c] The bioavailability of oral idarubicin is variable and is reported to be ~ 30% of the intravenous route. The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral idarubicin.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.29 Ifosfamide

RECOMMENDATION 4.29.1

We suggest the use of kidney function to inform the initial dosing of intravenous ifosfamide in all cancers. Kidney function may inform the monitoring of adverse events.

Ifosfamide, a prodrug, is activated in the liver by CYP450 enzymes to produce tautomeric intermediates and the metabolite chloroacetaldehyde, believed to be both neurotoxic and nephrotoxic.[508-510] The tautomeric intermediates are converted to alkylating toxic metabolites (i.e., acrolein) and inactive products.[508,511-514] The total recovery of ifosfamide in the urine has wide interpatient variability, with 11 – 82% of ifosfamide and its metabolites excreted in the urine.[508,512,514-518] Fractionation of ifosfamide dosing may result in auto-induction of its own metabolic pathway, causing increased formation of metabolites.[508,517,519-522]

Kidney function (eGFR range 33 – 125 mL/min/1.73 m^2) does not significantly influence the pharmacokinetics of ifosfamide (AUC, CL, V_d) or its inactive metabolites,[508] although a single case report observed accumulation of ifosfamide and the neurotoxic metabolite chloroacetaldehyde in a patient with acute kidney failure.[523]

Whilst some studies have observed no significant association between ifosfamide-related adverse events (i.e., central nervous system (CNS) neurotoxicity [encephalopathy], haematological toxicities [leucopenia, thrombocytopenia]) and kidney dysfunction (eGFR range 30 – 59 mL/min/1.73 m^2),[524,525] others have reported an increased risk of severe ifosfamide-related neurotoxicity with declining kidney function.[526-532] Additionally, the incidence of CNS neurotoxicity is increased in hypoalbuminaemia,[527-532] and poor performance status.[529] There is a paucity of ifosfamide toxicity data when eGFR < 30 mL/min/1.73 m^2.

Ifosfamide-related renal adverse events (i.e., AKI, proximal tubular dysfunction, tubulo-interstitial nephritis/fibrosis, glomerular dysfunction) are a common and sometimes irreversible dose-limiting toxicity, associated with an average eGFR decline of 15 mL/min/1.73 m^2 after first treatment, and occasionally resulting in KRT.[523,533-536] In addition to higher cumulative ifosfamide doses,[537,538] the risk of ifosfamide-related renal adverse events in adult populations is increased with concomitant nephrotoxic drug exposure (e.g., platinum drugs)[534-536] and prior nephrectomy.[536] Although the risk of ifosfamide-related renal adverse events has

not been correlated to baseline kidney function,[534] data did not include patients with pre-treatment eGFR ≤ 50 mL/min/1.73 m^2.

Haemorrhagic cystitis is a result of the toxic metabolite acrolein accumulating in the urine and damaging the bladder epithelium.[539-542] The effect of baseline kidney function on the risk of haemorrhagic cystitis is unclear, although adequate urine output to void the bladder of the urotoxic metabolite is necessary to prevent this adverse event.[513]

Evidence quality/certainty: ***low;*** *strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.29.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous ifosfamide in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of ifosfamide and the monitoring of adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies;*** *strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.29.3

We suggest an initial dose reduction of intravenous ifosfamide in kidney dysfunction in non-transplant settings*.

** For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring ifosfamide as part of their treatment. The dose adjustments have not been tailored for these protocols.*

In addition to the following recommendations, close monitoring for ifosfamide-related adverse events (i.e., CNS neurotoxicity [encephalopathy], haematological toxicities [leucopenia, thrombocytopenia], haemorrhagic cystitis) is advised where eGFR < 60 mL/min/1.73 m^2, given the increased potential of toxicities[526-532] and the additive clinical consequences of ifosfamide-induced renal adverse events on pre-existing kidney dysfunction.[534,535] Clinical consensus is to utilise fractionated ifosfamide treatment protocols where clinically appropriate, to maintain the renal excretion of ifosfamide and its metabolites, while reducing the risk of renal adverse events and development of related toxicities (CNS neurotoxicity [encephalopathy]).

For eGFR 45 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose ifosfamide. Whilst there may be an increased risk of ifosfamide-associated CNS neurotoxicity in this setting,[526-532] there is no substantial evidence that a dose reduction would reduce the risk of toxicity without compromising therapeutic efficacy.

For eGFR 15 – 44 mL/min/1.73 min^2, clinical consensus is to consider a 20% dose reduction or a clinically appropriate treatment protocol for patients with either a non-curative treatment intent, risk factors for ifosfamide-induced renal adverse events (i.e., concomitant nephrotoxic drug exposure,[534-536] prior nephrectomy[536]) or risk factors for ifosfamide-induced CNS neurotoxicity (i.e., hypoalbuminaemia,[527-532] poor performance status[529]), to decrease the risk of dose-limiting adverse events. A small study suggested a dose reduction of 20% may resolve severe ifosfamide-associated renal adverse events.[540] In patients with a curative treatment intent without risk factors for ifosfamide-related renal adverse events and CNS neurotoxicity, clinical consensus is to administer full dose. Whilst there may be an increased risk of ifosfamide-related CNS neurotoxicity in this cohort,[526-532] there is no substantial evidence that a dose reduction would reduce the risk of toxicity without compromising therapeutic efficacy.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- To reduce the risk of haemorrhagic cystitis from acrolein, adequate urine output and hydration during and after administration of intravenous ifosfamide is required.[513] Prophylactic administration of mesna and/or hyper-hydration is necessary to decrease the incidence of urothelial toxicity.[513,539,542-544] Local preventative hydration and mesna protocols should be followed.
- The dose reduction applies to each individual dose and not to the total number of days or duration of ifosfamide per treatment cycle.

Evidence quality/certainty: ***low;*** *strength of recommendation:* ***conditional****.*

Table 33 – Ifosfamide dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS IFOSFAMIDE DOSE RECOMMENDATIONS [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose [b,c]</td><td></td></tr>
<tr><td>45 – 59</td><td>full dose [b,c]</td><td>Potential for increased risk of adverse events (i.e., CNS neurotoxicity [encephalopathy], haematological toxicities [leucopenia, thrombocytopenia], renal adverse events, haemorrhagic cystitis).</td></tr>
<tr><td>30 – 44</td><td rowspan="2">reduce by 20% [b,c.d]
or
alternative protocol
or
full dose [b,c]</td><td>Consider a 20% dose reduction or clinically appropriate alternative treatment protocol in patients with either:
non-curative treatment intent
risk factors for renal adverse events (i.e., concomitant nephrotoxic drug exposure, prior nephrectomy)
risk factors for CNS neurotoxicity (i.e., hypoalbuminaemia, poor performance status)
In all other patients, consider full dose.

Potential for increased risk of adverse events (i.e., CNS neurotoxicity [encephalopathy], haematological toxicities [leucopenia, thrombocytopenia], renal adverse events, haemorrhagic cystitis).</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] For bone marrow transplantation conditioning, consult the transplant team if the patient has kidney dysfunction and is requiring ifosfamide as part of their treatment. The dose adjustments have not been tailored for these protocols.
[b] To maintain renal excretion of ifosfamide and its metabolites, reduce the risk of renal adverse events and development of related toxicities (CNS neurotoxicity [encephalopathy]), using fractionated ifosfamide treatment protocols is advised where clinically appropriate.
[c] Preventative and support care measures (as per local institutional policies) are advised in all patients to reduce the risk of haemorrhagic cystitis and include:
– adequate urine output and hydration during and after administration of intravenous ifosfamide
– prophylactic administration of mesna and/or hyper-hydration.
[d] The dose reduction applies to each individual dose and not to the total number of days or duration of ifosfamide per treatment cycle.</td></tr>
<tr><td colspan="3">Abbreviations; CNS, central nervous system; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.30 Irinotecan

RECOMMENDATION 4.30.1

We suggest the use of kidney function to inform the initial dosing of intravenous irinotecan in all cancers. Kidney function may inform the monitoring of adverse events.

Irinotecan, a prodrug, is hydrolysed to the active metabolite SN-38 which is further metabolised to the inactive glucuronide conjugate SN-38G.[545] Elimination of irinotecan and its metabolites is mainly biliary, however urinary excretion accounts for ~ 32% of the dose (~ 22% excreted as unchanged drug, ~ 3% as SN-38G and < 1% as SN-38).[546-549] SN-38 is highly protein bound (~ 99%), mostly to albumin.[550]

Kidney dysfunction (eGFR range 21 – 59 mL/min/1.73 m^2) does not significantly alter pharmacokinetic parameter estimates for irinotecan or its metabolites.[546,551,552] However patients with eGFR < 20 mL/min/1.73 m^2 (including patients undergoing KRT) have demonstrated significantly altered SN-38 pharmacokinetics (delayed elimination,[553] reduced CL,[554] increased C_{max},[554] increased unbound concentrations[555]) and increased SN-38/irinotecan AUC ratios,[554] compared to patients with normal kidney function.

There is limited evidence on the impact of kidney dysfunction on the incidence and severity of irinotecan-related adverse events. One study suggested a relationship between kidney function (eGFR range 35 – 66 mL/min/1.73 m^2) and the incidence and severity of irinotecan-related haematological toxicities (i.e., neutropenia), but not diarrhoea.[551] Several case studies report grade 4 toxicities (i.e., neutropenia, diarrhoea; rarely fatal) in patients with eGFR < 15 mL/min/1.73 m^2, despite reduced doses of irinotecan and/or with KRT.[553,556-558]

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.30.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous irinotecan in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of irinotecan and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.30.3

We suggest an initial dose reduction of intravenous irinotecan in kidney dysfunction.

In addition to the following recommendations, close monitoring for haematological toxicities is advised where eGFR < 60 mL/min/1.73 m^2 given the increased incidence and severity of neutropenia in this setting.[551,553,556-558]

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose irinotecan, given the lack of pharmacokinetic changes in this cohort and insufficient data to suggest a dose reduction will decrease the risk of irinotecan-related adverse events without compromising therapeutic efficacy.

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose irinotecan, given the absence of definitive evidence for the impact of dose reductions on adverse events and therapeutic efficacy in this setting. Where treatment intent is non-curative or the patient has a poor performance status, clinical consensus is to consider a 25% dose reduction to potentially reduce SN-38 systemic exposure and the risk of severe toxicities.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice point

- The dose reduction applies to each individual dose and not to the total number of days or duration of irinotecan per treatment cycle.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

Table 34 – Irinotecan dose recommendations according to kidney function

INTRAVENOUS IRINOTECAN DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**full dose**	Increased risk of adverse events (i.e., haematological toxicities [neutropenia]).
30 – 44		
15 – 29	**reduce by 25%**[a] **or** **full dose**	Consider a 25% dose reduction in patients with *either*: • non-curative treatment intent • a poor performance status. In all other patients, consider full dose. Increased risk of adverse events (i.e., haematological toxicities [neutropenia]).
< 15 (without KRT)	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	
KRT		

[a] The dose reduction applies to each individual dose and not to the total number of days or duration of irinotecan per treatment cycle.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.31 Lenalidomide

RECOMMENDATION 4.31.1

We recommend the use of kidney function to inform the initial dosing of oral lenalidomide in all cancers. Kidney function may inform the monitoring of adverse events.

Lenalidomide is eliminated primarily via urinary excretion, with ~ 84% of the dose recovered unchanged in urine within 24 hours in healthy adults (eGFR > 80 mL/min/1.73 m^2)[559-561] and ~ 43% when eGFR < 30 mL/min/1.73 m^2.[559] Given the renal CL of lenalidomide exceeds the GFR, it is believed that lenalidomide is also eliminated by active renal tubular secretion.[562]

Several pharmacokinetic studies have observed a proportional decrease in lenalidomide total and renal CL, prolonged t½, and increased AUC with decreasing kidney function.[559,562-566]

Higher incidences of lenalidomide-related grade ≥ 3 adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], infection) have been observed in patients with kidney dysfunction (eGFR < 60 mL/min/1.73 m^2, including in KRT) compared to normal kidney function.[567-570] Dose reductions, treatment interruptions and early treatment cessation secondary to adverse events are significantly more frequent with increasing severity of kidney dysfunction.[567,569,570] Renal adverse events (i.e., acute interstitial nephritis), although rare, have been reported with lenalidomide.[571,572]

Evidence quality/certainty: ***low****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.31.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral lenalidomide in kidney dysfunction.

A small number of studies have applied KDIGO CKD categories to guide dose adjustment of lenalidomide and the monitoring of adverse events.[567,568,570] Some studies, however, initiated lenalidomide dose adjustments when eGFR < 50 mL/min/1.73 m^2, instead of eGFR < 60 mL/min/1.73 m^2.[573-575] Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity. As such, lenalidomide dose adjustments are from eGFR < 60 mL/min/1.73 m^2, in line with the KDIGO CKD kidney dysfunction categories.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.31.3

We recommend an initial dose reduction of oral lenalidomide in kidney dysfunction.

In addition to the following recommendations, close monitoring for adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], infections) is advised where eGFR < 60 mL/min/1.73 m^2, given the evidence of higher lenalidomide systemic exposure[559,562-566] and increased incidence and severity of lenalidomide-related adverse events in kidney dysfunction.[567-570]

Pharmacokinetic studies have demonstrated the following dose adjustments based on kidney function achieve similar average daily lenalidomide systemic exposure (within +/- 25 % of the target AUC) across all kidney dysfunction groups,[559,563] and significantly reduce the incidence of lenalidomide-related adverse events to that of patients without kidney dysfunction.[563,573,574,576] Although some studies show similar therapeutic efficacy after application of these dose reductions,[563,574,577] others show inferior overall survival with declining kidney function.[567-570] Kidney dysfunction itself, however, is associated with a higher baseline mortality risk in multiple myeloma.[564,577-581] These dose adjustments are further supported by international consensus recommendations for multiple myeloma.[198]

For eGFR 30 – 59 mL/min/1.73 m^2, where lenalidomide starting dose in a protocol is:

1. **25 mg once daily**, an initial dose reduction to 10 mg once daily is recommended.

2. **10 mg once daily**, an initial dose reduction to 5 mg once daily is recommended.

For eGFR < 30 mL/min/1.73 m^2, where lenalidomide starting dose in a protocol is:

1. **25 mg once daily**, an initial dose reduction to 15 mg every 48 hours is recommended.

2. **10 mg once daily**, an initial dose reduction to 5 mg every 48 hours is recommended.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- Ensure further reductions are not applied to doses from treatment protocols that have already been adjusted based on performance status or age.[577,582]

- After initial lenalidomide dose adjustment, there should be a continuous process of dose adjustment considering variations in kidney function during treatment and drug tolerance.

- The dose reduction applies to each individual dose within the treatment cycle and not the total number of days or duration of lenalidomide per treatment cycle**.**

Evidence quality/certainty: ***low****; strength of recommendation:* ***strong****.*

Table 35 – Lenalidomide dose recommendations according to kidney function

<table>
<tr><th colspan="4">ORAL LENALIDOMIDE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th colspan="2">Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td colspan="2">full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="2"><u>When protocol starting dose is 25 mg daily</u>

reduce to 10 mg daily [a,b,c]</td><td rowspan="2"><u>When protocol starting dose is 10 mg daily</u>

reduce to 5 mg daily [a,b,c]</td><td rowspan="2">Increased risk for adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], infection).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td rowspan="2"><u>When protocol starting dose is 25 mg daily</u>

reduce to 15 mg every 48 hours [a,b,c]</td><td rowspan="2"><u>When protocol starting dose is 10 mg daily</u>

reduce to 5 mg every 48 hours [a,b,c]</td><td rowspan="2">Increased risk for adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], infection).</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="3">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing</td></tr>
<tr><td colspan="4">[a] Ensure further reductions are not applied to doses from treatment protocols that have already been adjusted based on performance status or age.
[b] After initial lenalidomide dose adjustment, there should be a continuous process of dose adjustment considering variations in kidney function during treatment and drug tolerance.
[c] The dose reduction applies to each individual dose and not to the total number of days or duration of lenalidomide per treatment cycle.</td></tr>
<tr><td colspan="4">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.32 Melphalan

RECOMMENDATION 4.32.1

We suggest the use of kidney function to inform the initial dosing of oral and intravenous melphalan in all cancers. Kidney function may inform the monitoring of adverse events.

Melphalan is eliminated by both renal excretion and spontaneous chemical degradation to non-cytotoxic active metabolites.[583] As melphalan is degraded rapidly in the urine, highly variable estimates of the fraction of melphalan that is renally excreted have been reported (range 2 – 92% excreted unchanged in urine within 6 hours).[584-590] Renal excretion of melphalan involves secretion and reabsorption by renal tubules.[589]

Several pharmacokinetic studies (including patients with eGFR < 15 mL/min/1.73 m^2) have demonstrated significantly reduced melphalan CL and increased systemic exposure (AUC) with declining kidney function,[586-588,591-598] thereby suggesting renal excretion is a major route of melphalan elimination. Although melphalan shows moderate to high binding to plasma proteins (54 – 94%), predominantly to albumin, hypoalbuminaemia does not significantly influence melphalan CL (total and unbound).[587-589,599] Additionally, paraprotein concentrations do not influence total or unbound melphalan pharmacokinetics.[588,599]

Higher incidences of melphalan-related grade ⩾ 3 adverse events (i.e., haematological toxicities [myelosuppression], infection-related deaths), dose reductions and early cessation of treatment have been reported with eGFR < 60 mL/min/1.73 m^2, with increasing frequency as kidney function declines further (eGFR < 30 mL/min/1.73 m^2).[600-602] Additionally, a significantly higher incidence of adverse events (i.e., infection,[600-605] diarrhoea[604] and grade ⩾ 3 mucositis[603,604,606]) has been reported with high-dose melphalan (≥ 140 mg/m^2) bone marrow transplant conditioning protocols in patients with eGFR < 60 mL/min/1.73 m^2 compared to normal kidney function, resulting in a prolonged length of hospital stay,[604,605] and prolonged duration of total parenteral nutrition.[604]

Renal adverse events (i.e., AKI, nephrotic syndrome) have been reported with melphalan treatment.[602,607,608] Several studies have suggested that baseline kidney dysfunction influences the risk of melphalan-related renal adverse events.[602,607,608]

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.32.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral and intravenous melphalan in kidney dysfunction.

A small number of studies have applied KDIGO CKD categories to guide the dose adjustment of melphalan and the monitoring of adverse events.[589,603,604] Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.32.3

We suggest an initial dose reduction of oral and intravenous melphalan in kidney dysfunction in non-transplant settings*.

** For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring melphalan as part of their treatment. The dose adjustments have not been tailored for these protocols.*

In addition to the following recommendations, close monitoring for melphalan-related adverse events (i.e., haematological toxicities [myelosuppression], infection, renal adverse events) is advised where eGFR < 60 mL/min/1.73 m^2, given the evidence of higher melphalan systemic exposure[586-588,591-598] and increased incidence and severity of adverse events in kidney dysfunction.[600-602]

When considering the dose recommendations below, it should be noted that the effect of melphalan dose adjustments on survival in multiple myeloma is uncertain given the pre-existing higher baseline mortality risk with kidney dysfunction in this cancer.[573,600,602]

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose melphalan given the absence of definitive evidence for the impact of dose reductions on survival outcomes and response rates. If the patient has either a poor performance status or concomitant nephrotoxic drug exposure, a 25% dose

reduction may be appropriate as supported by international consensus recommendations for multiple myeloma.[198]

For eGFR 15 – 29 mL/min/1.73 m^2, an initial dose reduction of melphalan by 50% is suggested to reduce the risk of grade ⩾ 3 melphalan-related adverse events, treatment interruptions or early cessation of treatment.[573,601]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- The bioavailability of oral melphalan is highly variable.[609] The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral melphalan.
- After initial melphalan dose adjustment, there should be a continuous process of dose adjustment considering variations in kidney function during treatment and drug tolerance.
- The dose reduction applies to each individual dose and not to the total number of days or duration of melphalan per treatment cycle.
- Dose adjustments of oral melphalan may require rounding to nearest tablet strength to enable delivery of a measurable dose.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 36 – Melphalan dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL and INTRAVENOUS MELPHALAN DOSE RECOMMENDATIONS [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="2">reduce by 25% [b,c,d]
or
full dose</td><td rowspan="2">Consider a 25% dose reduction in patients with either:
• a poor performance status
• concomitant nephrotoxic drug exposure.
In all other patients, consider full dose.

Increased risk for adverse events (i.e., haematological toxicities [myelosuppression], infection, renal adverse events).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>reduce by 50% [b,c,d]</td><td>Increased risk for adverse events (i.e., haematological toxicities [myelosuppression], infection, renal adverse events).</td></tr>
<tr><td>< 15
(without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring melphalan as part of their treatment. The dose adjustments have not been tailored for these protocols.
[b] The dose reduction applies to each individual dose and not to the total number of days or duration of melphalan per treatment cycle.
[c] After initial melphalan dose adjustment, there should be a continuous process of dose adjustment considering variations in kidney function during treatment and drug tolerance.
[d] The bioavailability of oral melphalan is highly variable. The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral melphalan.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.33 Mercaptopurine

RECOMMENDATION 4.33.1

We suggest the use of kidney function to inform the initial dosing of oral mercaptopurine in all cancers. Kidney function may inform the monitoring of adverse events.

Mercaptopurine is a prodrug that is biotransformed intracellularly via three main competing metabolic pathways to either cytotoxic 6-thioguanine nucleotides, or mostly inactive metabolites including 6-methylmercaptopurine (via thiopurine methyltransferase [TPMT], responsible for hepatotoxicity, gastrointestinal toxicities) or 6-thiouric acid (via xanthine oxidase).[610,611] Within 24 hours of orally administered mercaptopurine, ~ 7% of the dose is recovered in the urine as unchanged drug and ~ 27% as 6-thiouric acid.[612-614]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of mercaptopurine in cancer patients. A small study in renal transplant recipients receiving oral azathioprine (a prodrug of mercaptopurine) observed no correlation between kidney function (including when eGFR < 15 mL/min/1.73 m^2) and mercaptopurine systemic exposure (AUC, C_{max}).[615] However, due to large intra- and inter-individual variability in the systemic exposure of mercaptopurine and its active metabolites following oral administration,[613-616] the impact of kidney function on mercaptopurine pharmacokinetics is difficult to predict.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.33.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral mercaptopurine in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of mercaptopurine and the monitoring of adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional***.

RECOMMENDATION 4.33.3

We suggest an initial dose adjustment of oral mercaptopurine in kidney dysfunction.

Although small studies in paediatric patients with acute lymphoblastic leukaemia (eGFR > 60mL/min/1.73 m^2) have found an association between mercaptopurine AUC and rates of relapse,[617,618] an association between the oral dose of mercaptopurine and relapse rates has not been determined.[616] Given the large interindividual variability of mercaptopurine pharmacokinetics[613-616] (due to variable bioavailability[613,614] and metabolic enzyme activity[612,619-621]) and paucity of data in patients with eGFR < 60 mL/min/1.73 m^2, it is difficult to predict appropriate dose adjustments in patients with kidney dysfunction and their impact on toxicity or therapeutic efficacy. In addition to the following recommendations, close monitoring for potential mercaptopurine-related adverse events (i.e., haematological toxicities [myelosuppression], hepatotoxicity)[622,623] is advised where eGFR < 60 mL/min/1.73 m^2.

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose mercaptopurine. In patients with a poor performance status or concomitant nephrotoxic drug exposure, extending the dosing interval from 24 hours to 48 hours may be appropriate.

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to dose adjust by administering full dose and extending the dosing interval from 24 to 48 hours to prevent the potential accumulation of mercaptopurine and its active metabolites,

minimising the risk of mercaptopurine-related adverse events. For treatment protocols where mercaptopurine is administered three times per day,[624] a clinically appropriate alternative treatment protocol may be considered.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- Determining *TPMT* genotype or phenotype (enzyme activity) prior to commencement of mercaptopurine is advised by regulatory bodies, as low TPMT enzyme activity significantly increases the risk of mercaptopurine-related severe and life-threatening myelosuppression as mercaptopurine is pushed down the active metabolite pathway.[619,621,625,626] Doses may require additional adjustment based on TPMT genotype / phenotype.[626]

- Concomitant xanthine oxidase inhibitor (e.g., allopurinol,[622] methotrexate[627]) administration pushes metabolism of mercaptopurine down the active metabolite pathway, increasing exposure to cytotoxic activity, and potentially leading to increased therapeutic efficacy and/or toxicity.[628] Consider the indication for concomitant xanthine oxidase inhibitor administration before applying any mercaptopurine dose adjustment to avoid toxicity.

- If the adjusted dose is tolerated (noting that steady state is reached in 2 to 4 weeks, and large interindividual variability exists in achieving a therapeutic AUC), dose titration (as guided by treatment protocol) may be considered on subsequent cycles, with careful monitoring for adverse events (i.e., haematological toxicities [myelosuppression] and hepatotoxicity).

- Dose adjustment applies to each individual dose and not the total number of days or duration of mercaptopurine per treatment cycle.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

Table 37 – Mercaptopurine dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL MERCAPTOPURINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose [a,b]</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="2">extend dosing interval [a,b,c,d]
or
full dose [a,b]</td><td rowspan="2">Consider dose adjustment by extending the dosing interval from 24 to 48 hours in patients with either:
• a poor performance status
• concomitant nephrotoxic drug exposure.
In all other patients, proceed with full dose.

Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression], hepatotoxicity).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>extend dosing interval [a,b.c.d]
or
alternative protocol</td><td>Consider dose adjustment by extending the dosing interval from 24 to 48 hours.
Where the mercaptopurine dosing schedule is three times per day, consider a clinically appropriate alternative treatment protocol
Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression], hepatotoxicity).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] Testing for TPMT enzyme genetic polymorphisms prior to commencement of mercaptopurine is advised. Doses may require additional adjustment based on TPMT enzyme activity, to reduce the risk of severe and life-threatening myelosuppression.
[b] Concomitant xanthine oxidase inhibitor (e.g., allopurinol, methotrexate) administration may increase formation of cytotoxic metabolite, potentially leading to increases in therapeutic efficacy and/or toxicity. Consider the indication for concomitant xanthine oxidase inhibitor administration before applying any mercaptopurine dose adjustment to avoid toxicity.
[c] If the adjusted dose is tolerated (noting that steady state is reached in 2 to 4 weeks), dose titration (as guided by treatment protocol) may be considered on subsequent cycles, with careful monitoring for adverse events.
[d] Dose adjustment applies to each individual dose and not the total number of days or duration of mercaptopurine per treatment cycle.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy; TPMT, thiopurine methyltransferase gene.</td></tr>
</table>

4.34 Methotrexate

RECOMMENDATION 4.34.1

We recommend the use of kidney function to inform the initial dosing of oral and intravenous methotrexate in all cancers. Kidney function may inform the monitoring of adverse events.

Methotrexate, although active itself, undergoes liver biotransformation to the major inactive metabolite 7-hydroxy-methotrexate, and intracellular conversion to active methotrexate polyglutamates.[629] Methotrexate polyglutamates are more cytotoxic than the parent drug, but only form after at least 6 hours of intracellular exposure to ≥ 2 µmol/L of methotrexate.[630] High doses of methotrexate (≥ 500 mg/m^2) aim to increase penetration into sanctuary sites (i.e., CNS, testes) particularly with shorter infusions, or enhance cytotoxicity through the formation of polyglutamates with longer infusions.[631] Renal excretion is the major route of elimination (~ 80%) for methotrexate and 7-hydroxy-methotrexate, involving glomerular filtration, tubular secretion and tubular reabsorption.[632-635] At plasma concentrations of ≥ 0.1 – 0.4 µmol/L, active reabsorption becomes saturated and tubular secretion predominates.[636]

Pharmacokinetic studies in < 500 mg/m^2 methotrexate and high-dose (≥ 500 mg/m^2) methotrexate treatment protocols have demonstrated significantly reduced methotrexate and 7-hydroxy-methotrexate CL (renal and total CL), prolonged elimination t½, and increased systemic exposure (AUC) with decreasing kidney function (including eGFR < 15 mL/min/1.73 m^2).[632,634,637-642]

The risk of severe methotrexate-related adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis], hepatotoxicity) is significantly increased in the setting of kidney dysfunction (including eGFR < 15 mL/min/1.73 m^2) due to reduced drug elimination resulting in prolonged exposure and elevated plasma concentrations.[642-645] At high doses, methotrexate and 7-hydroxy-methotrexate precipitate in renal tubules, causing tubular injury and a decline in kidney function, contributing to dose-limiting toxicities.[639,640] The risk of methotrexate-induced AKI increases with prolonged elevated plasma methotrexate concentrations, pre-existing kidney dysfunction, concomitant nephrotoxic drug exposure, acidic urine (decreases solubility of parent drug and metabolites, thereby reducing excretion) and volume depletion.[639,640,646-649]

Calcium folinate (leucovorin) rescue therapy is routinely commenced 24 – 36 hours following high-dose methotrexate administration to reduce treatment-related toxicities by replenishing depleted folate, without compromising anticancer activity.[650] Even with appropriate preventative and supportive care measures, the risk of high-dose methotrexate-induced AKI (≥ grade 2) in eGFR ≥ 30 mL/min/1.73 m^2 is 1.8% in patients with osteosarcoma and 9 – 15% in patients with lymphoma, with severe complications and death occurring in a subset of these patients.[648,651,652]

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

RECOMMENDATION 4.34.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral and intravenous methotrexate in kidney dysfunction.

A small number of studies have applied KDIGO CKD categories to the dose adjustment of methotrexate and the monitoring of adverse events.[216,642] Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.34.3

We recommend an initial dose reduction of oral and intravenous methotrexate in kidney dysfunction in non-transplant settings*.

** For bone marrow transplantation protocols involving graft versus host disease prophylaxis, consult the transplant team if the patient has kidney dysfunction and is requiring methotrexate as part of their treatment. The dose adjustments have not been tailored for these protocols.*

There is a lack of definitive evidence for the impact of dose adjustments on methotrexate systemic exposure, toxicity, and therapeutic efficacy in eGFR < 60 mL/min/1.73 m^2. In addition to the following recommendations, close monitoring for methotrexate-related adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis], AKI) is advised in kidney dysfunction.

Directly measured GFR is preferred to guide the initial dose adjustment of oral and intravenous methotrexate in kidney dysfunction.

To ensure therapeutic dosing and to reduce the incidence of methotrexate-related adverse events, clinical consensus is that directly measured GFR is preferred for initial dosing especially where:

- eGFR is < 60 mL/min/1.73 m^2
- methotrexate doses are ≥ 500 mg/m^2
- eGFR may be unreliable in specific clinical circumstances (e.g., extremes of body composition, amputees, paraplegia, conditions of skeletal muscle).

For eGFR 45 – 59 mL/min/1.73 m^2, where the methotrexate starting dose in a protocol is:

1. **< 500 mg/m^2**, where there is curative intent, and the patient has both a poor performance status and concomitant nephrotoxic drug exposure, clinical consensus is to consider a clinically appropriate alternative treatment protocol. In all other patients, consider reducing the dose of methotrexate by 25%. In breast cancer patients with eGFR 45 – 59 mL/min/1.73 m^2 receiving a 15 – 50% dose reduction, the incidence and severity of treatment-related adverse events and response rates were comparable to patients receiving full dose methotrexate with normal kidney function,[216,475,653] although overall survival may be reduced.[26] Dose reductions between 37.5 – 62.5% in bladder cancer patients with eGFR 45 – 59 mL/min/1.73 m^2 resulted in comparable toxicities (i.e., haematological, gastrointestinal [nausea/vomiting]) and response rates to patients with normal kidney function receiving full dose (50 mg/m^2) methotrexate, however overall survival was not reported.[290] While toxicity may

be manageable with dose reduction, bladder cancer patients with eGFR < 60 mL/min/1.73m^2 and poor performance status did not benefit from a 50% dose reduction of methotrexate in combination therapy (poor therapeutic efficacy and increased toxicity) and it was suggested alternative treatment should be considered in such patients.[654]

2. **≥ 500 mg/m^2**, where there is curative intent, and the patient has both a good performance status and no concomitant exposure to nephrotoxic drugs, clinical consensus is to administer full dose methotrexate. This is of particular importance in primary CNS lymphoma where an exposure threshold (AUC > 1100 µmol*hr/L or ≥ 3000 mg/m^2 doses) was independently associated with better overall survival in eGFR 50 – 59 mL/min/1.73 m^2,[644] and is further supported by international guidelines.[655] Methotrexate efficacy and toxicity outcomes in primary CNS lymphoma were comparable in patients with normal kidney function receiving full doses (8000 mg/m^2) and in patients with eGFR 50 – 59 mL/min/1.73 m^2 maintaining the exposure threshold (AUC) of ≥ 3000 mg/m^2 (despite dose attenuation to 3500 – 4800 mg/m^2).[656] In other haematological malignancies, no significant differences in survival outcomes have been observed in patients with eGFR 50 – 59 mL/min/1.73 m^2 administered full dose methotrexate (1000 mg/m^2) and those with eGFR 45 – 50 mL/min/1.73 m^2 receiving a 25% dose reduction of methotrexate as part of the hyper-CVAD protocol.[341] However, increases in the incidence of febrile neutropenia requiring further dose reductions of methotrexate have been reported in this cohort, and may limit the ability to deliver high-intensity chemotherapy in these patients (especially in those with a poor performance status).[341,657,658] For patients with either a non-curative treatment intent, poor performance status or concomitant nephrotoxic drug exposure, clinical consensus is to reduce the methotrexate dose by 25% or a consider a clinically appropriate alternative treatment protocol given altered pharmacokinetics[639-642] and the anticipated increased incidence of methotrexate-related adverse events in this cohort.[341,642,644,657,658]

For eGFR 30 – 44 mL/min/1.73 m^2, for patients with a curative treatment intent, or in patients with both a poor performance status and concomitant nephrotoxic drug exposure, clinical consensus is to consider a clinically appropriate alternative treatment protocol.[654] For all other patients, reduce the dose by 50% for both < 500 mg/m^2 and high-dose (≥ 500 mg/m^2) methotrexate protocols. In patients with eGFR < 40 mL/min/1.73 m^2, a 25% dose reduction for < 500 mg/m^2 methotrexate was insufficient at preventing dose delays due to myelosuppression (potentially fatal) in 90% of patients,[475] however a 50% dose reduction was proposed to sufficiently reduce toxicity.[637] Dose reductions between 25 – 75% in both < 500 mg/m^2 and high-dose methotrexate protocols have demonstrated a similar incidence and severity of treatment-related toxicities compared to patients with normal kidney function receiving full doses.[216,290,475,653,654] The consequences of methotrexate dose

reductions on survival outcomes in this cohort is unclear, with several studies reporting no change,[216,341,475] whilst others demonstrate poorer efficacy.[653,654,657,658]

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to avoid methotrexate and use a clinically appropriate alternative treatment protocol. Increases in methotrexate AUC (associated with reduced CL and prolonged elimination t½) are expected in this cohort,[632,634,637-642] and there is a lack of evidence for the impact of dose adjustment on the incidence of adverse events or therapeutic efficacy. Although several studies in haematological malignancies have applied 50% dose reductions for 24-hour infusions of high-dose methotrexate in eGFR 10 – 50 mL/min/1.73 m^2, toxicity and efficacy outcomes were not stratified by eGFR < 30 mL/min/1.73 m^2 and ≥ 30 mL/min/1.73 m^2.[341,658]

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- In **all patients**, to minimise the risk of methotrexate-induced AKI, preventative measures are advised:
  - Avoidance of concomitant administration of drugs that inhibit renal tubular secretion and/or have additive nephrotoxic potential (especially for 24 hours either side of methotrexate doses).[650,659,660]
  - Drainage off third-space effusions prior to treatment to prevent methotrexate distribution to these compartments and subsequent delay of elimination.[650,659,660]
  - Monitoring of kidney function before, during and after methotrexate administration to identify signs of kidney function deterioration.[659]
- In patients receiving **high-dose methotrexate (≥ 500 mg/m^2)**, additional supportive care measures are required to minimise the risk of methotrexate-induced AKI:
  - Maintaining intravenous hydration, adequate urinary output, fluid balance and urinary alkalinisation (pH > 7) before, during and after methotrexate administration as per treatment protocol.[649,650,659,660]
  - Pharmacokinetically-guided calcium folinate (leucovorin) rescue, starting 24 – 36 hours post methotrexate infusion (as per treatment protocol) until plasma methotrexate concentrations are at least < 0.1 µmol/L by 72 hours.[650,659,660]

  - Monitoring of methotrexate plasma concentrations every 24 hours from the end of the methotrexate infusion, with prompt intervention (including consultation with clinical pharmacology) if plasma concentrations are elevated at 48 hours (as per nomogram) to avoid life-threatening toxicity.[650,660] Interventions may include intensification of calcium folinate (leucovorin), glucarpidase and/or dialysis, but are dependent on the time since methotrexate infusion, kidney function and timely access to the intervention.[650,660-662]

- The bioavailability of oral methotrexate is highly variable and dose dependent.[663] The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral methotrexate.

- The dose reduction applies to each individual dose within the treatment cycle. For a continuous infusion, the dose reduction refers to the total dose and not the total duration of the infusion per treatment cycle**.**

- Dose adjustments may require rounding to nearest tablet strength to enable delivery of a measurable dose.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 38 – Methotrexate dose recommendations according to kidney function

<table>
<tr><th colspan="4">ORAL and INTRAVENOUS METHOTREXATE DOSE RECOMMENDATIONS [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th colspan="2">Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td colspan="2">full dose [b,c,d]</td><td></td></tr>
<tr><td>45 – 59</td><td><u>When protocol starting dose is < 500 mg/m²</u>

alternative protocol

or

reduce by 25% [b,c,e,f,g]</td><td><u>When protocol starting dose is ≥ 500 mg/m²</u>

full dose [b,c,d]

or

reduce by 25% [b,c.d,f]

or

alternative protocol</td><td>In < 500 mg/m², consider a clinically appropriate alternative treatment protocol in patients with:
• <u>curative</u> treatment intent, and
• poor performance status, and
• concomitant nephrotoxic drug exposure.
In all other patients, consider a 25% dose reduction.

In ≥ 500 mg/m², consider full dose in patients with:
• <u>curative</u> treatment intent, where maintaining an exposure threshold is required (i.e., primary CNS lymphoma), and
• good performance status, and
• no concomitant nephrotoxic drug exposure
In all other patients, consider a 25% dose reduction or a clinically appropriate alternative treatment protocol.

Increased risk of adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis], AKI).</td></tr>
<tr><td>30 – 44</td><td colspan="2">alternative protocol

or

reduce by 50% [b,c,d,e,f,g]</td><td>Consider a clinically appropriate alternative treatment protocol in patients with a <u>curative</u> treatment intent or in patients with:
• poor performance status, and
• concomitant nephrotoxic drug exposure
In all other patients, consider a 50% dose reduction.

Increased risk of adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis], AKI).</td></tr>
<tr><td>15 – 29</td><td colspan="2" rowspan="2">AVOID</td><td rowspan="2">Not recommended – use a clinically appropriate alternative treatment protocol.</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="3">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
</table>

[a] For bone marrow transplantation protocols involving graft versus host disease prophylaxis, consult the transplant team if the patient has kidney dysfunction and is requiring methotrexate as part of their treatment. The dose adjustments have not been tailored for these protocols.

[b] To ensure therapeutic dosing and reduce the incidence of methotrexate-related adverse events, directly measured GFR is preferred for the initial dosing especially where *either*:

- eGFR is < 60 mL/min/1.73 m^2
- Methotrexate doses are ≥ 500 mg/m^2
- eGFR may be unreliable in specific clinical circumstances (e.g., extremes of body composition, amputees, paraplegia, conditions of skeletal muscle).

Measured GFR refers to a direct measurement of the clearance of exogenous markers such as iohexol, iothalamate, 51Cr-EDTA (radioactive chromium complex with ethylenediaminetetraacetic acid) or ^{99}Tc-DTPA (TC-diethylenetriaminepentaacetic acid).

[c] The following preventative measures are advised to minimise methotrexate-induced AKI in all patients:

- Avoid concomitant use of drugs that impair renal elimination of methotrexate or have additive nephrotoxic potential (especially 24 hours either side of methotrexate doses)
- Drain third space effusions prior to treatment
- Monitor kidney function before, during and after methotrexate administration.

[d] For doses ≥ 500 mg/m^2 additional supportive care measures are required to minimise methotrexate-indued AKI:

- Maintain intravenous hydration, adequate urinary output, fluid balance and urinary alkalinisation (pH > 7) before, during and after methotrexate administration as per treatment protocol.
- Use pharmacokinetically-guided calcium folinate (leucovorin) rescue starting 24-36 hours post methotrexate infusion (as per treatment protocol) until plasma methotrexate concentrations are at least < 0.1 µmol/L by 72 hours.
- Monitor methotrexate plasma concentrations every 24 hours from the end of the methotrexate infusion, with prompt intervention if plasma concentrations are high at 48 hours (as per nomogram) to avoid life-threatening toxicity.

[e] The bioavailability of oral methotrexate is highly variable and dose dependent. The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral methotrexate.

[f] The dose reduction applies to each individual dose within the treatment cycle. For a continuous infusion, the dose reduction refers to the total dose and not the total duration of the infusion per treatment cycle**.**

[g] Dose adjustments may require rounding to nearest tablet strength to enable delivery of a measurable dose.

Abbreviations: AKI – acute kidney injury; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.35 Mitomycin

RECOMMENDATION 4.35.1

We suggest the use of kidney function to inform the initial dosing of intravenous mitomycin in all cancers. Kidney function may inform the monitoring of adverse events.

Mitomycin (also known as mitomycin C), is primarily eliminated via hepatic metabolism, with < 20% of the administered dose excreted unchanged in the urine within 24 hours.[664-667] Since metabolic pathways are saturated at relatively low doses, the percentage of a dose excreted in urine increases with increasing doses.[666]

There is a paucity of published evidence on the impact of kidney dysfunction on the pharmacokinetics and clinical outcomes of mitomycin. In a small pharmacokinetic study, mitomycin pharmacokinetics (CL, AUC, $t_{1/2}$) were unaffected by S_{Cr}.[664] Another small study observed a similar incidence of haematological toxicities, however an increased potential of gastrointestinal toxicities (i.e., nausea and vomiting), in patients with eGFR < 25 mL/min/1.73 m^2 versus those with normal kidney function receiving mitomycin.[668]

Haemolytic uremic syndrome (HUS), involving AKI-associated microangiopathic haemolytic anaemia and thrombocytopenia, is an uncommon, but severe and potentially fatal, renal adverse event observed with mitomycin treatment.[669-674] The decline in kidney function is often delayed, progressive and irreversible, necessitating KRT in up to a third of patients.[675] The risk of mitomycin-related HUS is correlated to cumulative mitomycin dose,[669,672,674,676] with an incidence of 2% in patients receiving cumulative doses of < 50 mg/m^2 compared to 11% at cumulative doses 50 – 70 mg/m^2.[674] It is unclear if baseline kidney dysfunction influences the risk of HUS with mitomycin treatment.

Evidence quality/certainty: ***low;*** *strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.35.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous mitomycin in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of mitomycin and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

*Evidence quality/certainty**: no studies;** strength of recommendation**: conditional**.*

RECOMMENDATION 4.35.3

We suggest an initial dose reduction of intravenous mitomycin in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose mitomycin. To reduce the risk of severe mitomycin-related HUS, avoid exceeding a cumulative total mitomycin dose of 40 mg/m^2.[669,671,672,674,676] Given the lack of substantial data on pharmacokinetic changes and clinical outcomes of mitomycin in this cohort, close monitoring for potential adverse events (i.e., HUS, gastrointestinal toxicities [nausea and vomiting])[668] is advised.

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to avoid mitomycin and use a clinically appropriate alternative treatment protocol. There is a paucity of pharmacokinetic, safety and efficacy data in patients with eGFR < 30 mL/min/1.73 m^2, and currently no substantial evidence to suggest that mitomycin dose reductions in this cohort will reduce the risk of adverse events without compromising therapeutic efficacy.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 39 – Mitomycin dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS MITOMYCIN DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose [a]</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="2">full dose [a]</td><td rowspan="2">Potential for increased risk of adverse events (i.e., HUS, gastrointestinal toxicities [nausea and vomiting]).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td rowspan="2">AVOID</td><td rowspan="2">Not recommended - use a clinically appropriate alternative treatment protocol.</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">[a] To prevent HUS, avoid exceeding total cumulative mitomycin dose of 40 mg/m^2.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; HUS, haemolytic uremic syndrome; KRT, kidney replacement therapy.</td></tr>
</table>

4.36 Nivolumab

RECOMMENDATION 4.36.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous nivolumab in all cancers.

Nivolumab has a large molecular weight (~ 144 kDa) and therefore is unlikely to undergo glomerular filtration or urinary excretion.[677] Protein catabolism via endocytosis (receptor-mediated or reticuloendothelial cells) is the expected mechanism of nivolumab elimination.[677]

Kidney function does not significantly influence nivolumab pharmacokinetics (CL, minimum concentration [C_{min}]),[678-680] although evidence is lacking where eGFR < 30 mL/min/1.73 m^2. Nivolumab appears to be well tolerated in patients with kidney dysfunction, including in patients with eGFR < 15 mL/min/1.73 m^2 requiring KRT, with a low incidence of grade ≥ 3 or treatment-limiting toxicities.[681-688] A single centre retrospective study, however, observed a greater incidence of all grade haematological toxicities with immune checkpoint inhibitor treatment where eGFR < 15 mL/min/1.73m^2.[689]

Immune-related renal adverse events have been observed with nivolumab treatment, and commonly involve AKI leading to acute interstitial nephritis, acute tubular injury or glomerular diseases.[409,411,685,687,690-693] The impact of baseline kidney dysfunction on the risk of immune-related renal adverse events with nivolumab is unclear, with some studies reporting no association[409,411,690,693] and another observing an increased risk of immune-checkpoint inhibitor-associated AKI with declining kidney function.[407]

A higher risk of graft rejection has been observed in kidney transplant patients (especially allografts) receiving nivolumab (pooled kidney transplant rejection rate of 67%).[413,694] The likelihood of graft rejection versus the possible therapeutic benefits of nivolumab needs to be carefully considered in such cases.[416]

For eGFR < 60 mL/min/1.73 m^2, full dose nivolumab is recommended.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice point

- In accordance with international guidelines,[416] measuring baseline kidney function, electrolyte levels and urinalysis are advised before commencement and as clinically indicated throughout nivolumab treatment to monitor for developing immune-related renal adverse events. This is particularly pertinent in patients with additional risk factors for developing immune-related AKI (i.e., concomitant nephrotoxic drug exposure, combination immune checkpoint inhibitor therapy, dehydration, pre-existing hypertension).[407,409,411,690,693]

Evidence quality/certainty: ***very low****; strength of recommendation:* ***strong****.*

Table 40 – Nivolumab dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS NIVOLUMAB DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose [a]</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">[a] Measurement of baseline kidney function, electrolyte levels and urinalysis are advised before commencement and as clinically indicated throughout nivolumab treatment to monitor for developing immune-related renal adverse events. This is particularly pertinent in patients with additional risk factors for developing immune-related AKI (i.e., concomitant nephrotoxic drug exposure, combination immune checkpoint inhibitor therapy, dehydration, pre-existing hypertension).</td></tr>
<tr><td colspan="3">Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.37 Obinutuzumab

RECOMMENDATION 4.37.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous obinutuzumab in all cancers. Kidney function may inform the monitoring of adverse events and the selection of an alternative treatment protocol.

Obinutuzumab has a large molecular weight (~ 146 kDa)[695] and is therefore unlikely to undergo glomerular filtration or urinary excretion. The pharmacokinetics (CL, V_d, AUC) of obinutuzumab do not appear to be significantly influenced by kidney function when eGFR > 60 mL/min/1.73 m^2,[696,697] although pharmacokinetic studies in kidney dysfunction are limited.

Obinutuzumab appears to be well tolerated and efficacious in haematological malignancies where eGFR < 60 mL/min/1.73 m^2,[698-702] although there is a paucity of data in cancer patients with eGFR < 30 mL/min/1.73 m^2.[700] Several studies have described a higher incidence of obinutuzumab-related grade ≥ 3 infusion-related reactions,[698] TLS,[702] and infections[702] in patients with eGFR 30 – 70 mL/min/1.73 m^2 and with a poorer performance status especially when given in combination with other anticancer drugs.[698,702]

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose obinutuzumab. Close monitoring for adverse events (i.e., infusion-related reactions, TLS, infections) is advised, especially in patients with additional TLS risk factors, a poor performance status, or receiving concomitant anticancer drugs.

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to consider a clinically appropriate alternative treatment protocol given the lack of pharmacokinetic and toxicity data in this cohort. If an alternative protocol is not suitable, clinical consensus is to administer full dose obinutuzumab with close monitoring for adverse events (i.e., infusion-related reactions, TLS, infections), especially in patients with additional TLS risk factors, a poor performance status, or receiving concomitant anticancer drugs.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- To minimise the risk of severe infusion-related reactions, adequate preventative measures[703,704] are advised (as per local institutional protocols) and include:
  - premedication with an antipyretic, corticosteroid, and antihistamine
  - dividing the infusion of large doses over two days during the first cycle
  - close monitoring of vital signs before, during and after the infusion
  - gradually increasing the infusion rate as tolerated for the first cycle

- To minimise the risk of TLS in eGFR < 60 mL/min/1.73 m^2, adequate preventative measures[705] are advised (as per local institutional protocols) and include:
  - intravenous hydration
  - early administration of anti-hyperuricaemics
  - close laboratory and clinical monitoring for TLS.

Evidence quality/certainty: ***low****; strength of recommendation:* ***strong****.*

Table 41 – Obinutuzumab dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS OBINUTUZUMAB DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose [a]</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="2">full dose [a,b]</td><td rowspan="2">Increased risk of adverse events (i.e., infusion-related reactions, TLS, infections), especially in patients with either:
additional TLS risk factors
poor performance status
concomitant anticancer drug exposure.</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>alternative protocol
or
full dose [a,b]</td><td>Consider a clinically appropriate alternative treatment protocol.

If an alternative protocol is not suitable and proceeding with obinutuzumab, consider full dose.

Increased risk of adverse events (i.e., infusion-related reactions, TLS, infections), especially in patients with either:
additional TLS risk factors
poor performance status
concomitant anticancer drug exposure.</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] To minimise the risk of severe infusion-related reactions, adequate preventative measures are advised (as per local institutional protocols) and include:
– premedication with an antipyretic, corticosteroid, and antihistamine
– dividing the infusion of large doses over two days during the first cycle
– close monitoring of vital signs before, during and after the infusion
– gradually increasing the infusion rate as tolerated for the first cycle.
[b] To minimise the risk of TLS, adequate preventative measures are advised (as per local institutional protocols) and include:
– intravenous hydration
– early administration of anti-hyperuricaemics
– close laboratory and clinical monitoring for TLS.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy; TLS – tumour lysis syndrome.</td></tr>
</table>

4.38 Oxaliplatin

RECOMMENDATION 4.38.1

We suggest the use of kidney function to inform the initial dosing of intravenous oxaliplatin in all cancers. Kidney function may inform the monitoring of adverse events.

Oxaliplatin undergoes rapid non-enzymatic biotransformation into numerous active and inactive metabolites that are further processed and eliminated primarily in the urine.[706] It is estimated that up to 40% of oxaliplatin is eliminated in the urine over 48 hours,[707-712] with a reduced contribution of renal CL as kidney function declines (eGFR 20 – 59 mL/min/1.73 m^2).[711,712] Oxaliplatin is highly protein bound (~ 65 – 95%), mostly to plasma proteins and erythrocytes,[713,714] and has a large V_d, influencing the availability of free platinum (unbound active drug).[714]

Oxaliplatin CL is correlated with kidney function,[707,712,714] with significantly lower CL (of both total and free platinum), and higher free platinum systemic exposure (AUC) reported in patients with kidney dysfunction (including eGFR < 20 mL/min/1.73 m^2) when compared to patients with eGFR ≥ 60 mL/min/1.73 m^2.[707,711,712,714,715]

Despite this correlation, a significant increase in grade ≥ 3 oxaliplatin-related adverse events was not observed in patients with kidney dysfunction (eGFR 20 – 59 mL/min/1.73 m^2) exposed to higher plasma concentrations (AUC).[707,711,712,714] A potentially increased incidence of gastrointestinal toxicities (i.e., nausea and vomiting) requiring dose adjustment, treatment interruption or hospitalisation has been observed when oxaliplatin is administered concurrently with renally excreted anticancer drugs in kidney dysfunction.[213,716] Numerous studies have reported a comparable incidence of oxaliplatin-related neurotoxicity (i.e., peripheral neuropathy) and grade ≥ 3 haematological adverse events (i.e., thrombocytopenia, neutropenia) in patients with and without kidney dysfunction,[213,711,712,714,716-718] although data in patients with eGFR < 15 mL/min/1.73 m^2 is limited to very small sample sizes.[711,712]

Renal adverse events (i.e., AKI involving tubular necrosis, tubulointerstitial nephritis, renal tubular vacuolisation, proximal renal tubular acidosis, and immune-related haemolytic anaemia),[709,719-735] while rare, have been reported with oxaliplatin treatment, although the association with baseline kidney dysfunction is unclear.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.38.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous oxaliplatin in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of oxaliplatin and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.38.3

We suggest an initial dose reduction of intravenous oxaliplatin in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, full dose oxaliplatin is suggested. There is no substantial evidence to suggest a dose reduction of oxaliplatin will reduce the risk of oxaliplatin-related adverse events without compromising therapeutic efficacy.[213] Despite changes in oxaliplatin pharmacokinetic parameters (AUC, CL, V_d) in patients with eGFR 30 – 59 mL/min/1.73 m^2 receiving reduced doses, the incidence of grade ≥ 3 toxicities (i.e., haematological toxicities [thrombocytopenia, neutropenia], neurotoxicity [e.g., peripheral neuropathy]) were similar to patients who received full dose.[711,712]

For eGFR 15 – 29 mL/min/1.73 m^2, in patients with a curative intent, clinical consensus is to consider full dose oxaliplatin or a clinically appropriate alternative treatment protocol as there is limited evidence on appropriate oxaliplatin dose adjustments and subsequent clinical outcomes in this cohort. A single study involving a small number of patients with eGFR 20 – 30 mL/min/1.73 m^2 observed comparable incidences of grade ≥ 3 or dose-limiting toxicities (i.e., neurotoxicity [peripheral neuropathy], haematological toxicities [thrombocytopenia, neutropenia]) between patients administered full dose or 20 – 40% dose reductions, despite altered AUC.[711] However, one patient with eGFR < 20 mL/min/1.73 m^2, was excluded from the final study analysis because of treatment-limiting toxicity, despite receiving a ~ 60% dose reduction of oxaliplatin.[711] In patients with either a poor performance status, concomitant nephrotoxic drug exposure or a non-curative intent, clinical consensus is that a dose reduction of 50% may be appropriate to reduce the likelihood of oxaliplatin-related adverse events. Close monitoring for oxaliplatin-related adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia], neurotoxicity [peripheral neuropathy], gastrointestinal toxicities [nausea and vomiting]) is advised for all patients given the lack of substantial evidence in this cohort.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 42 – Oxaliplatin dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS OXALIPLATIN DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>full dose

or

alternative protocol

or

reduce by 50%</td><td>Consider full dose or a clinically appropriate alternative treatment protocol in patients with a curative treatment intent.

Consider a 50% dose reduction in patients with either:
non-curative treatment intent
poor performance status
concomitant nephrotoxic drug exposure.
Potential for increased risk of adverse events (i.e., haematological toxicities [thrombocytopenia, neutropenia], neurotoxicity [peripheral neuropathy], gastrointestinal toxicities [nausea and vomiting]).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.39 Paclitaxel

RECOMMENDATION 4.39.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous paclitaxel in all cancers. Kidney function may inform the monitoring of adverse events.

Paclitaxel is extensively metabolized in the liver by CYP450 enzymes to largely inactive hydroxylated metabolites.[736-740] Elimination is primarily via biliary excretion, with ~ 5% of the administered dose excreted in urine as unchanged drug within 24 hours.[741-746] Although paclitaxel is highly protein bound (88 – 98%), with albumin and α_1-acid glycoprotein contributing equally to overall binding,[742,745-748] hypoalbuminaemia has not been associated with significant changes in paclitaxel pharmacokinetics.[749]

There is limited published evidence regarding the effects of kidney dysfunction on paclitaxel pharmacokinetics. In a patient with an eGFR of 20 mL/min/1.73 m^2, a 1.5-fold increase in both systemic exposure (AUC) and elimination $t_{1/2}$ were observed in comparison to patients with normal kidney function.[741] In contrast, several case reports in patients with eGFR < 15 mL/min/1.73 m^2 receiving KRT have observed comparable paclitaxel pharmacokinetics (C_{max}, AUC, CL) to those in patients with normal kidney function at similar doses, despite negligible removal of paclitaxel by dialysis.[750-753]

No significant differences in the frequency of paclitaxel-related adverse events (i.e., haematological toxicities [leucopenia, neutropenia, anaemia], neurotoxicity [peripheral neuropathy]) have been observed in patients with eGFR 30 – 59 mL/min/1.73 m^2 versus normal kidney function.[754] Case reports in patients with eGFR < 15 mL/min/1.73 m^2 (including in KRT) have demonstrated that full dose paclitaxel was well tolerated, with no dose-limiting or treatment-limiting toxicities.[750,752,753,755,756]

There is limited evidence on the efficacy of paclitaxel in patients with kidney dysfunction, however, some studies suggest there are similar outcomes in patients with eGFR < 60 mL/min/1.73 m^2 versus those with normal kidney function.[496,754]

For eGFR 15 – 59 mL/min/1.73 m^2, full dose paclitaxel is recommended.

For eGFR < 15 mL/min/1.73 m^2, full dose paclitaxel is recommended, with close monitoring for adverse events (i.e., haematological toxicities [leucopenia, neutropenia, anaemia], neurotoxicity [peripheral neuropathy]) due to the paucity of

data in this setting.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 43 – Paclitaxel dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS PACLITAXEL DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="4">full dose</td><td rowspan="4"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td><td>full dose</td><td>Potential for increased risk of adverse events (i.e., haematological toxicities [leucopenia, neutropenia, anaemia], neurotoxicity [peripheral neuropathy]).</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.40 Nanoparticle Albumin-Bound Paclitaxel

RECOMMENDATION 4.40.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous nanoparticle albumin-bound paclitaxel (nab-paclitaxel) in all cancers. Kidney function may inform the monitoring of adverse events.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is primarily eliminated via hepatic metabolism and biliary excretion[757] with ~ 4% of the administered dose excreted unchanged in the urine.[758]

Kidney function (eGFR range ≥ 30 mL/min/1.73 m^2) does not significantly influence nab-paclitaxel elimination[759] or the incidence and severity of treatment-related adverse events (i.e., haematological toxicities [leucopenia, neutropenia, anaemia], neurotoxicity [peripheral neuropathy], arthralgia, fatigue).[759,760] Additionally, the incidence of toxicity-related dose reductions, treatment interruptions and survival outcomes among patients receiving nab-paclitaxel appear independent of kidney function (eGFR ≥ 30 mL/min/1.73 m^2).[760] There is a paucity of data on the incidence of nab-paclitaxel-related adverse events and on the pharmacokinetic profile of nab-paclitaxel where eGFR < 30 mL/min/1.73 m^2.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.40.2

We suggest the use of KDIGO CKD categories to guide monitoring for intravenous nanoparticle albumin-bound paclitaxel (nab-paclitaxel) adverse events in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide monitoring of nab-paclitaxel-related adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.40.3

We suggest *against* an initial dose reduction of intravenous nanoparticle albumin-bound paclitaxel (nab-paclitaxel) in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, full dose nab-paclitaxel is suggested due to the lack of significant changes in elimination or risk of adverse events compared to eGFR ≥ 60 mL/min/1.73 m^2.[759,760]

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose nab-paclitaxel, with close monitoring for adverse events (i.e., haematological toxicities [leucopenia, neutropenia, anaemia], neurotoxicity [peripheral neuropathy], arthralgia, fatigue) given the paucity in pharmacokinetic and toxicity data in this cohort.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional****.*

Table 44 – Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS NAB-PACLITAXEL DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>full dose</td><td>Potential for increased risk of adverse events (i.e., haematological toxicities [leucopenia, neutropenia, anaemia], neurotoxicity [peripheral neuropathy], arthralgia, fatigue).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.41 Panitumumab

RECOMMENDATION 4.41.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous panitumumab in all cancers.

Panitumumab has a large molecular weight (~ 147 kDa) and is therefore unlikely to undergo glomerular filtration or urinary excretion.[761] Receptor-mediated endocytosis and the reticuloendothelial system are the primary mechanisms of panitumumab elimination.[761]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of panitumumab treatment. In a population pharmacokinetic analysis, kidney function (eGFR range 30 – 80 mL/min/1.73 m^2) had no clinically meaningful impact on panitumumab pharmacokinetics (C_{min}, C_{max}, CL).[762] A single case report of panitumumab in a patient with an eGFR of 11 mL/min/1.73 m^2 showed a comparable pharmacokinetic profile to historical controls in patients without kidney dysfunction.[763] Case reports in patients with eGFR < 30 mL/min/1.73 m^2 (including KRT) have also demonstrated that conventional panitumumab dosing (6 mg/kg) was well tolerated, with no treatment-limiting toxicities.[763,764]

Although renal adverse events (i.e., hypomagnesaemia, hypokalaemia, AKI, diffuse proliferative glomerulonephritis, nephrotic syndrome, hypoalbuminaemia) have been reported with panitumumab treatment,[251,253,255,765-767] baseline kidney dysfunction does not appear to influence their risk of occurrence.[255]

For eGFR < 60 mL/min/1.73 m^2, full dose panitumumab is recommended.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 45 – Panitumumab dose recommendations according to kidney function

INTRAVENOUS PANITUMUMAB DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59		
30 – 44		
15 – 29		
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.42 Pembrolizumab

RECOMMENDATION 4.42.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous pembrolizumab in all cancers.

Pembrolizumab has a large molecular weight (~ 149 kDa) and is therefore unlikely to undergo glomerular filtration or urinary excretion.[768] Protein catabolism via the reticuloendothelial system or target-mediated disposition are the primary mechanisms of pembrolizumab elimination.[768]

The pharmacokinetics of pembrolizumab (CL, AUC) do not appear to be significantly influenced by kidney function (including where eGFR < 15 mL/min/1.73 m^2).[679,769,770] Pembrolizumab appears to be well tolerated in patients with kidney dysfunction, including in patients with eGFR < 15 mL/min/1.73 m^2 requiring KRT, with a low incidence of grade ≥ 3 or treatment-limiting toxicities.[682,683,685,771-775] A single centre retrospective study, however, observed a greater incidence of haematological adverse events with immune checkpoint inhibitor treatment where eGFR < 15 mL/min/1.73 m^2.[689]

Immune-related renal adverse events have been observed with pembrolizumab treatment, and commonly involve AKI leading to acute interstitial nephritis, acute tubular injury or glomerular diseases.[407,409,411,685,690,692,693,776] The impact of baseline kidney dysfunction on the risk of immune-related renal adverse events with pembrolizumab is unclear, with some studies reporting no association[409,411,690,693] and another observing an increased risk of immune-checkpoint inhibitor-associated AKI with declining kidney function.[407]

A higher risk of graft rejection has been observed in kidney transplant patients (especially allografts) receiving pembrolizumab (pooled kidney transplant rejection rate of 55%).[413,777,778] The likelihood of graft rejection versus the possible therapeutic benefits of pembrolizumab needs to be carefully considered in such cases.[416]

For eGFR < 60 mL/min/1.73 m^2, full dose pembrolizumab is recommended.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice point

- In concordance with international guidelines,[416] measuring baseline kidney function, electrolyte levels and urinalysis are advised before commencement and as clinically indicated throughout pembrolizumab treatment to monitor for developing immune-related renal adverse events. This is particularly pertinent in patients with additional risk factors for developing immune-related AKI (i.e., concomitant nephrotoxic drug exposure, combination immune checkpoint inhibitor therapy, dehydration, pre-existing hypertension).[407,409,411,690,693]

Evidence quality/certainty: ***low****; strength of recommendation:* ***strong***.

Table 46 – Pembrolizumab dose recommendations according to kidney function

INTRAVENOUS PEMBROLIZUMAB DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose** [a]	
45 – 59		
30 – 44		
15 – 29		
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

[a] Measurement of baseline kidney function, electrolyte levels and urinalysis are advised before commencement and as clinically indicated throughout pembrolizumab treatment to monitor for developing immune-related renal adverse events. This is particularly pertinent in patients with additional risk factors for developing immune-related AKI (i.e., concomitant nephrotoxic drug exposure, combination immune checkpoint inhibitor therapy, dehydration, pre-existing hypertension).

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.43 Pemetrexed

RECOMMENDATION 4.43.1

We suggest the use of kidney function to inform the initial dosing of intravenous pemetrexed in all cancers. Kidney function may inform the monitoring of adverse events.

Pemetrexed is primarily eliminated by the kidneys, with 70 – 90% excreted unchanged in the urine within 24 hours after administration, through both tubular secretion and glomerular filtration.[779-782] Severe kidney dysfunction (eGFR < 20 mL/min/1.73 m^2) may result in delayed renal excretion.[783] Although pemetrexed is moderately bound to plasma proteins (73 – 81%),[781,783] the unbound fraction is not significantly influenced by kidney function (eGFR range 19 – 151 mL/min/1.73 m^2).[781,783] Redistribution of pemetrexed to extravascular compartments (i.e., third-space effusions) may prolong terminal $t_{1/2}$.[779,784]

Kidney function (including eGFR < 15 mL/min/1.73 m^2) influences pemetrexed pharmacokinetics, with decreased kidney function associated with significantly reduced pemetrexed total and renal CL, prolonged elimination $t_{1/2}$ and increased AUC.[779,780,782-786]

When eGFR < 45 mL/min/1.73 m^2, an increased incidence and severity of pemetrexed-related haematological (i.e., neutropenia, anaemia) and non-haematological (i.e., nausea) adverse events have been observed.[785,787-789] One death as a result of pemetrexed-related toxicities (haematological toxicities [neutropenia, thrombocytopenia], fatigue/weakness, gastrointestinal toxicities [mucositis]) has been reported in a patient with eGFR 19 mL/min/1.73 m^2.[783] Concomitant nephrotoxic drug exposure (i.e., platinum agents, non-steroidal anti-inflammatory drugs) may be a risk factor for pemetrexed-related adverse events.[790,791]

Pemetrexed-related renal adverse events (i.e., AKI, acute tubular necrosis, interstitial nephritis, distal renal tubular acidosis, nephrogenic diabetes insipidus)[782,784,792-800] have been observed and may be associated with an increased severity of pemetrexed-related haematological adverse events[784,793,798] and an increased incidence of dose reductions/interruptions or early treatment cessation.[801-803] The mechanism of pemetrexed's nephrotoxicity is likely related to accumulation in renal tubular cells during active tubular secretion.[782,797,798] Risk factors for pemetrexed-related renal adverse events include baseline kidney dysfunction,[782,788,796,802,803] cumulative pemetrexed dose (> 6 cycles),[12,25] and administration of concomitant nephrotoxic agents.[784,801]

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional***.

RECOMMENDATION 4.43.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous pemetrexed in kidney dysfunction.

A small number of studies have applied partial KDIGO CKD categories to guide dose adjustment of pemetrexed and the monitoring of adverse events.[788-790,796] Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional***.

RECOMMENDATION 4.43.3

We suggest an initial dose reduction of intravenous pemetrexed in kidney dysfunction.

In addition to the following recommendations, close monitoring of pemetrexed-related adverse events (i.e., haematological toxicities [neutropenia, anaemia], gastrointestinal toxicities [mucositis, nausea], renal adverse events) is advised in kidney dysfunction, particularly when eGFR < 45 mL/min/1.73 m^2.[782,783,785,787-789,796,802,803]

For eGFR 45 – 59 mL/min/1.73 m^2, full dose pemetrexed is suggested. Despite a modest reduction in pemetrexed CL and increase in systemic exposure in patients with eGFR 40 – 59 mL/min/1.73 m^2 versus normal kidney function,[779,780,783] the incidence of pemetrexed-related severe and dose-limiting adverse events were comparable between groups in the presence of folic acid and vitamin B_{12} supplementation.[783]

For eGFR 30 – 44 mL/min/1.73 m^2, an initial dose reduction of pemetrexed by 20% is suggested. Significant increases in systemic exposure[779,780,785,786] and incidences of grade ≥ 3 adverse events[783,785,787-789] have been observed with full dose pemetrexed when eGFR < 45 mL/min/1.73 m^2. One study in patients with eGFR 20 – 44 mL/min/1.73 m^2 receiving a 20% pemetrexed dose reduction observed a comparable incidence of grade ≥ 3 adverse events to historical controls with normal kidney function receiving full dose.[789,790] Limited data exists for the impact of dose reductions on survival, with a single case report indicating therapeutic efficacy can be maintained with a 20% dose reduction and an increased dosing interval from 3 to 4 weeks.[804] For patients with either a non-curative treatment intent, a poor performance status or concomitant nephrotoxic drug exposure,[790,791] clinical consensus is to consider an alternative treatment protocol given the paucity of data in this cohort.

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to avoid pemetrexed and use a clinically appropriate alternative treatment protocol, given the altered pharmacokinetics (CL, AUC),[779,785,786] increased incidence of pemetrexed-related adverse events,[783,785,788,789] and insufficient evidence on the impact of dose reductions on survival outcomes in this cohort. A 20% dose reduction was inadequate in reducing the incidence of grade ≥ 3 haematological adverse events when eGFR < 30 mL/min/1.73 m^2.[790] Cases of treatment-limiting neuropathy[786] and fatal grade 4 haematological toxicities[783] have been reported in patients with eGFR < 20 mL/min/1.73 m^2 receiving pemetrexed, even with a 70 – 80% dose reduction. Pemetrexed dose reductions in eGFR ≤ 20 mL/min/1.73 m^2 aiming to achieve a similar AUC as found in normal kidney function, were unable to decrease the

incidence of grade ≥ 3 adverse events.[785] A 13-fold reduction of the target AUC was needed to decrease neutropenic events comparable to patients with normal kidney function receiving full dose pemetrexed.[785]

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- Administration of folic acid and vitamin B_{12} supplementation prior to, and during, pemetrexed administration is advised in all patients to reduce the risk of severe dose-limiting toxicities.[783,785]

- To minimise the risk of pemetrexed-induced renal adverse events (and to prevent subsequent toxicities due to kidney dysfunction), preventative measures are advised:

  - Where possible, avoid concomitant administration of drugs that inhibit renal tubular secretion and/or have additive nephrotoxic potential (e.g., non-steroidal anti-inflammatories) before and after pemetrexed infusions[781,791]
  - Consider drainage of third-space effusions prior to treatment to prevent pemetrexed distribution into these compartments and subsequent delay of elimination[781,805,806]

Evidence quality/certainty: ***low****; strength of recommendation:* ***conditional***.

Table 47 – Pemetrexed dose recommendations according to kidney function

INTRAVENOUS PEMETREXED DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose** [a]	
45 – 59	**full dose** [a]	Increased risk of adverse events (i.e., haematological toxicities [neutropenia, anaemia], gastrointestinal toxicities [mucositis, nausea], renal adverse events)
30 – 44	**alternative protocol** **or** **reduce by 20%** [a]	Consider a clinically appropriate alternative treatment protocol in patients with *either*: • non-curative treatment intent • a poor performance status • concomitant nephrotoxic drug exposure In all other patients, consider a 20% dose reduction. Increased risk of adverse events (i.e., haematological toxicities [neutropenia, anaemia], gastrointestinal toxicities [mucositis, nausea], renal adverse events).
15 – 29	**AVOID**	Not recommended – use a clinically appropriate alternative treatment protocol.
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

[a] The following preventative and supportive care measures are advised in all patients to reduce the risk of pemetrexed-related adverse events:
- supplementation with folic acid and vitamin B_{12} before and during pemetrexed infusions
- avoidance of concomitant drugs that impair renal elimination of pemetrexed and/or have additive nephrotoxic potential (e.g., NSAIDs) before and after pemetrexed infusions
- drainage of third space effusions prior to treatment to avoid prolonged exposure.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

4.44 Pertuzumab

RECOMMENDATION 4.44.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous pertuzumab in all cancers.

Pertuzumab has a large molecular weight (~ 148 kDa) and is therefore unlikely to undergo glomerular filtration or urinary excretion.[807] Elimination is through the reticuloendothelial system.[807]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of pertuzumab treatment. In a population pharmacokinetic analysis, S_{Cr} had no statistically significant impact on pertuzumab CL or V_d.[808] Case reports in patients with eGFR < 15 mL/min/1.73 m^2 requiring KRT have observed that full dose pertuzumab maintained therapeutic efficacy and was well tolerated, with no dose-limiting or grade ≥ 3 toxicities.[809-811]

Renal adverse events (i.e., AKI, hypokalaemia), although rare, have been reported with pertuzumab treatment.[253] It is unclear whether baseline kidney dysfunction influences the risk of pertuzumab-related renal adverse events.

For eGFR < 60 mL/min/1.73 m^2, full dose pertuzumab is suggested.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 48 – Pertuzumab dose recommendations according to kidney function

INTRAVENOUS PERTUZUMAB DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59		
30 – 44		
15 – 29		
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.45 Procarbazine

RECOMMENDATION 4.45.1

We suggest the use of kidney function to inform the initial dosing of oral procarbazine in all cancers. Kidney function may inform the monitoring of adverse events.

Procarbazine is a pro-drug requiring hepatic conversion by CYP450 enzymes and monoamine oxidase to the active metabolites azo-procarbazine and methylazoxy-procarbazine.[812,813] Approximately 70% of the administered dose is excreted by the kidneys, primarily in the form of an inactive metabolite (~ 5% as unchanged drug).[812,813]

There is a paucity of data on the pharmacokinetics and clinical outcomes of procarbazine in kidney dysfunction, with only limited evidence suggesting full dose procarbazine in patients with eGFR 40 – 59 mL/min/1.73 m^2 is unlikely to increase the incidence of adverse events.[814,815] Several case reports in Hodgkin lymphoma patients with renal parenchymal infiltration and eGFR < 22 mL/min/1.73 m^2 have demonstrated procarbazine-containing treatment protocols can be administered at full dose without an increase in treatment-limiting toxicities (i.e., haematological toxicities [myelosuppression], hepatotoxicity), resulting in improved kidney function with disease control.[816,817]

Procarbazine may compete with other drugs predominantly cleared by the kidney as described by a small case series where AKI occurred in patients receiving both procarbazine and high-dose methotrexate who initially had normal kidney function.[818]

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.45.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of oral procarbazine in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of procarbazine and the monitoring of adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

*Evidence quality/certainty**: no studies**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.45.3

We suggest an initial dose reduction of oral procarbazine in kidney dysfunction.

For eGFR 45 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose procarbazine, given there is unlikely to be an increased risk of adverse events in patients with eGFR > 40 mL/min/1.73 m^2.[814,815] There is currently no evidence to suggest there are significant pharmacokinetic changes in this cohort.

For eGFR 15 – 45 mL/min/1.73 m^2, clinical consensus is to administer full dose procarbazine with close monitoring for a potential increase in adverse events (i.e., haematological toxicities [myelosuppression], hepatotoxicity). There is currently no substantial evidence to suggest dose reductions will lessen the anticipated increase in procarbazine-related adverse events or pharmacokinetic changes without adversely impacting therapeutic efficacy. A case report in a patient with eGFR 17 mL/min/1.73 m^2 demonstrated full dose procarbazine could be administered as part of the BEACOPP regimen without an increase in grade ≥ 3 procarbazine-related adverse events.[816] Consider a 25% dose reduction where there is either non-curative treatment intent, a poor performance status or concomitant nephrotoxic drug exposure.[818]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Practice points

- The dose reduction applies to each individual dose and not to the total number of days or duration of procarbazine per treatment cycle.
- Dose adjustments may require rounding to nearest capsule strength to enable delivery of a measurable dose.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

Table 49 – Procarbazine dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL PROCARBAZINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="2">full dose</td><td rowspan="2"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td><td rowspan="2">reduce by 25% [a,b]

or

full dose</td><td rowspan="2">Consider a 25% dose reduction in patients with either:
• non-curative treatment intent
• a poor performance status
• concomitant nephrotoxic drug exposure.
In all other patients, consider full dose.

Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression], hepatotoxicity).</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] Dose adjustments may require rounding to nearest capsule strength to enable delivery of a measurable dose.
[b] The dose reduction applies to each individual dose and not to the total number of days or duration of procarbazine per treatment cycle.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.46 Raltitrexed

RECOMMENDATION 4.46.1

We recommend the use of kidney function to inform the initial dosing of intravenous raltitrexed in all cancers. Kidney function may inform the monitoring of adverse events.

Raltitrexed is primarily metabolised intracellularly to produce polyglutamate metabolites, with 40 – 50% of raltitrexed excreted unchanged in the urine.[819-821] Raltitrexed is highly protein bound to albumin (93%) and extensively distributed in tissues,[821,822] with extensive polyglutamation resulting in slow redistribution of raltitrexed from the tissue into the plasma and a prolonged elimination half-life.[819,823]

Reduced kidney function (eGFR range 25 – 65 mL/min/1.73 m^2) has been associated with significant changes in raltitrexed pharmacokinetics, with decreased CL, prolonged elimination $t_{1/2}$ and increased AUC in comparison to patients with normal kidney function.[823,824] Given that raltitrexed is highly protein bound, patients with low albumin concentrations are potentially at increased risk of raltitrexed-related adverse events because of higher levels of free unbound raltitrexed.[823]

One study observed a higher incidence of grade ≥ 3 adverse events (i.e., haematological toxicities [leucopenia, anaemia], infection, gastrointestinal toxicities [nausea and vomiting, diarrhoea, mucositis], dermatological toxicities [skin rash]) and hospitalisations due to adverse events in patients with eGFR 25 – 65 mL/min/1.73 m^2 in comparison to patients with normal kidney function.[822]

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

RECOMMENDATION 4.46.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous raltitrexed in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of raltitrexed and the monitoring of adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.46.3

We recommend an initial dose adjustment of intravenous raltitrexed in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, clinical consensus is for a dose reduction of 50% and extending the dosing interval from 21 days to 28 days. Extensive polyglutamation causing the slow redistribution of raltitrexed from tissues into the plasma,[819,823] and the changes in raltitrexed pharmacokinetics (reduced CL, prolongation of elimination $t_{1/2}$) in this cohort,[823,824] increase the risk of drug accumulation during three-weekly administration of raltitrexed. The effect of dose reduction on the therapeutic efficacy of raltitrexed is unclear. Due to the potential for an increased risk of raltitrexed-related grade ≥ 3 adverse events (i.e., haematological toxicities [leucopenia, anaemia], infection, gastrointestinal toxicities [nausea and vomiting, diarrhoea, mucositis], dermatological toxicities [skin rash]) in patients with eGFR 30 – 59 mL/min/1.73 m^2,[822] close monitoring for these toxicities is advised.

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to avoid raltitrexed and use a clinically appropriate alternative treatment protocol. There is a paucity of pharmacokinetic, toxicity and efficacy data in patients with an eGFR < 25 mL/min/1.73 m^2, and currently no substantial evidence to suggest that raltitrexed dose reductions in this cohort reduce the risk of adverse events without compromising therapeutic efficacy.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Evidence quality/certainty: ***moderate****; strength of recommendation:* ***strong****.*

Table 50 – Raltitrexed dose recommendations according to kidney function

INTRAVENOUS RALTITREXED DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**adjust dose**	Consider a 50% dose reduction and extension of the dosing interval from 21 days to 28 days. Potential for increased risk of adverse events (i.e., haematological toxicities [leucopenia, anaemia], gastrointestinal toxicities [nausea and vomiting, diarrhoea, mucositis], dermatological toxicities [skin rash]).
30 – 44		
15 – 29	**AVOID**	Not recommended – use a clinically appropriate alternative treatment protocol.
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.47 Rituximab

RECOMMENDATION 4.47.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous or subcutaneous rituximab in all cancers.

Rituximab has a large molecular weight (~ 144 kDa)[825] and is therefore unlikely to undergo glomerular filtration or urinary excretion.

The systemic exposure of rituximab does not appear to be significantly influenced by kidney function (in non-nephrotic patients),[826] although data when eGFR < 30 mL/min/1.73 m^2 is limited to a single case report.[827] In patients with nephrotic syndrome and associated severe proteinuria, altered rituximab pharmacokinetics (decreased AUC, shorter $t_{1/2}$, increased CL and evidence of urinary rituximab elimination) has been reported, due to compromised glomerular membrane permeability allowing proteins with large molecular weights to be excreted in the urine.[828-830] The applicability of these findings to cancer populations is unknown. Consider the clinical implications of altered exposure when administering rituximab in cancer patients with nephrotic syndrome and associated severe proteinuria.

Although studies are limited, rituximab appears to be as well tolerated and as efficacious in haematological malignancies where eGFR < 60 mL/min/1.73 m^2 compared to normal kidney function.[317,831-834] Several studies in patients with systemic autoimmune diseases have reported a trend for a higher rate of adverse events (including grade ≥ 3 infections) with rituximab treatment in patients with an eGFR < 45 mL/min/1.73 m^2,[835,836] however this was not observed in a cancer population.[317]

For eGFR < 60 mL/min/1.73 m^2, full dose rituximab is suggested.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 51 – Rituximab dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS and SUBCUTANEOUS RITUXIMAB DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.48 Temozolomide

RECOMMENDATION 4.48.1

We suggest *against* the use of kidney function to inform the initial dosing of oral temozolomide in all cancers. Kidney function may inform the monitoring of adverse events.

Temozolomide is a prodrug which undergoes pH-dependent conversion to the active 3-methyl(triazen-1-yl) imidazole-4-carboxamide (MTIC) with further degradation of MTIC acting as the principal pathway for temozolomide elimination.[837-839] Urinary excretion of temozolomide is ~ 38%, with ~ 6% excreted as unchanged drug and ~ 32% as other metabolites.[837-840]

The pharmacokinetics of temozolomide (CL, V_d, C_{max}, AUC) and MTIC (AUC) do not appear to be influenced by kidney dysfunction,[841-844] although studies in eGFR < 30 mL/min/1.73 m^2 are lacking.

There is limited published evidence regarding the effects of kidney dysfunction on temozolomide adverse events and therapeutic efficacy. Studies in patients with eGFR < 60 mL/min/1.73 m^2 (including those undergoing KRT) observed a comparable degree of temozolomide-related adverse events (i.e., haematological toxicities [lymphopenia, thrombocytopenia, neutropenia], infections) as patients with normal kidney function.[845-848]

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.48.2

We suggest the use of KDIGO CKD categories to guide monitoring for oral temozolomide-related adverse events in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide monitoring of temozolomide-related adverse events. Clinical consensus is that standardisation of kidney dysfunction categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.48.3

We suggest *against* an initial dose reduction of oral temozolomide in kidney dysfunction.

For eGFR 30 – 59 mL/min/1.73 m^2, full dose temozolomide is suggested due to the lack of significant changes in pharmacokinetics in this cohort compared to eGFR ≥ 60 mL/min/1.73 m^2.[841,843,844]

For eGFR 15 – 29 mL/min/1.73 m^2, clinical consensus is to administer full dose temozolomide but with close monitoring for temozolomide-related adverse events (i.e., haematological toxicities [lymphopenia, thrombocytopenia, neutropenia], infections), given the insufficient pharmacokinetic data in this cohort. There is currently no substantial evidence that a dose reduction will result in a reduced risk of adverse events without compromising therapeutic efficacy in patients with kidney dysfunction.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

Evidence quality/certainty: ***very low****; strength of recommendation:* ***conditional****.*

Table 52 – Temozolomide dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL TEMOZOLOMIDE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="3">full dose</td><td rowspan="3"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td>full dose</td><td>Potential for increased risk of adverse events (i.e., haematological toxicities [lymphopenia, thrombocytopenia, neutropenia], infections).</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.49 Thalidomide

RECOMMENDATION 4.49.1

We recommend *against* the use of kidney function to inform the initial dosing of oral thalidomide in all cancers. Kidney function may inform the monitoring of adverse events.

Thalidomide undergoes biotransformation by non-enzymatic hydrolysis in the liver to multiple inactive metabolites,[849] with < 1% of the administered dose recovered in the urine as unchanged thalidomide within 24 hours.[850]

Thalidomide pharmacokinetics (AUC, V_d and CL) are not significantly influenced by kidney function (including eGFR < 15 mL/min/1.73 m^2, with or without KRT).[851-853]

The incidence of thalidomide-related adverse events and associated dose reductions, treatment interruptions and early treatment cessation are similar in patients with kidney dysfunction (eGFR range 7 – 57 mL/min/1.73 m^2) and with normal kidney function.[573,854,855] However, unexplained severe hyperkalaemia has been occasionally observed with thalidomide treatment in patients with eGFR < 30 mL/min/1.73 m^2, particularly those undergoing KRT.[856,857]

Although some studies show inferior overall survival and response rates with thalidomide treatment as kidney function declines,[573,855] kidney dysfunction itself is associated with a higher baseline mortality risk in multiple myeloma.[578-580]

For eGFR < 60 mL/min/1.73 m^2, full dose thalidomide is recommended. This is further supported by international consensus recommendations for multiple myeloma.[198] Close monitoring for hyperkalaemia is advised where eGFR < 30 mL/min/1.73 m^2.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 53 – Thalidomide dose recommendations according to kidney function

ORAL THALIDOMIDE DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59		
30 – 44		
15 – 29	**full dose**	Potential for increased risk of hyperkalaemia.
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.50 Thiotepa

RECOMMENDATION 4.50.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous thiotepa in non-transplant settings*. Kidney function may inform the monitoring of adverse events.

** For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring thiotepa as part of their treatment. The dose adjustments have not been tailored for these protocols.*

Thiotepa undergoes hepatic metabolism by CYP450 enzymes to the major active metabolite triethylenephosphoramide (TEPA), which has comparable alkylating activity to thiotepa.[858] In adult patients with normal kidney function receiving 40 to 60 mg/m^2 of intravenous thiotepa, < 2% of the administered dose is excreted in the urine as unchanged thiotepa and ~ 11% as TEPA (or ~ 4% if administered lower doses e.g., 12 mg/m^2).[859-862]

The effects of kidney dysfunction on thiotepa pharmacokinetics and resulting clinical outcomes have not been adequately investigated. Pharmacokinetic studies observing no significant relationship between kidney function and CL of thiotepa and TEPA have not included patients with an eGFR < 60 mL/min/1.73 m^2.[863,864] A single case report of high-dose thiotepa (60 mg/m^2), cyclophosphamide and carboplatin administration in a patient with eGFR of 38 mL/min/1.73 m^2 described reduced CL and increased elimination $t_{1/2}$ of thiotepa, resulting in higher thiotepa and TEPA exposure (AUC increased 1.4- and 2.6-fold, respectively) relative to a reference population with normal kidney function).[314] A 30% dose reduction of thiotepa was insufficient in reducing the AUC to that observed in patients with normal kidney function receiving full dosing.[314]

For eGFR 15 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose thiotepa but with close monitoring for adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis], infections) due to the paucity of pharmacokinetic and toxicity data in this cohort.

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **very low**; strength of recommendation: **conditional**.*

Table 54 – Thiotepa dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS THIOTEPA DOSING RECOMMENDATION [a]</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="3">full dose</td><td rowspan="3">Potential for increased risk of adverse events (i.e., haematological toxicities [myelosuppression], gastrointestinal toxicities [mucositis], infection).</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15 (without KRT)</td><td colspan="2" rowspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td>KRT</td></tr>
<tr><td colspan="3">[a] For bone marrow transplantation conditioning protocols, consult the transplant team if the patient has kidney dysfunction and is requiring thiotepa as part of their treatment. The dose adjustments have not been tailored for these protocols.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.51 Topotecan

RECOMMENDATION 4.51.1

We recommend the use of kidney function to inform the initial dosing of intravenous topotecan in all cancers. Kidney function may inform the monitoring of adverse events.

Topotecan undergoes reversible, pH-dependent hydrolysis of its lactone ring (active form) to its inactive hydroxy-acid form.[865] A small amount of topotecan is also converted into the active metabolite N-desmethyl topotecan in the liver, however the clinical significance of this metabolite is unknown.[865,866]

Topotecan is largely excreted via the kidneys, with ~ 20 – 68% found in urine as parent drug (either lactone ring or hydroxy-acid forms)[865-871] and < 5% as the active metabolite N-desmethyl topotecan within 24 hours.[865,866] High inter-individual variability in the urinary excretion of topotecan has been observed, likely due to the unstable nature of topotecan.[866,867,869,871] Given the renal CL of topotecan exceeds GFR, topotecan may also be eliminated by renal tubular secretion.[872-876]

Topotecan pharmacokinetics demonstrate large inter-individual variability. Several pharmacokinetic studies have observed significantly reduced topotecan CL,[872-875,877,878] prolonged elimination $t_{1/2}$,[872,875,879] and potential increases in systemic exposure (AUC, C_{max})[878,879] in association with decreasing kidney function (including eGFR < 15 mL/min/1.73 m^2, with and without KRT).

Kidney dysfunction (including eGFR < 15 mL/min/1.73 m^2) has been associated with a significantly increased incidence of potentially fatal topotecan-related grade ≥ 3 haematological toxicities (i.e., thrombocytopenia, neutropenia), requiring dose adjustment.[875,878,880] The risk of non-haematological toxicities (i.e., gastrointestinal toxicity) appears to be independent of kidney function, except fatigue which has been observed more frequently in patients with kidney dysfunction.[875,879]

Evidence quality/certainty: ***low;*** *strength of recommendation:* ***strong****.*

RECOMMENDATION 4.51.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous topotecan in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of topotecan and the monitoring of adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

*Evidence quality/certainty**: no studies;** strength of recommendation**: conditional**.*

RECOMMENDATION 4.51.3

We recommend an initial dose reduction of intravenous topotecan in kidney dysfunction.

In addition to the following recommendations, close monitoring for adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], fatigue) is advised where eGFR is < 60 mL/min/1.73 m^2 given the evidence of increased toxicities in this cohort.[874,875,879,880]

For eGFR 45 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose topotecan, given the absence of definitive evidence for the impact of dose reductions on therapeutic efficacy in this cohort. Consider a 30% dose reduction in patients with either a poor performance status,[873,878,880] concomitant nephrotoxic drug exposure or extensive prior therapy (including, but not limited to, previous exposure to platinum therapy[878,880] or alkylating agents,[869,875] ≥ 2 successive protocols in the preceding 6 months,[874] or large field radiation to areas containing bone marrow[869,875,880]) as these cohorts have demonstrated a reduced topotecan CL[878] and a higher incidence and severity of grade ≥ 3 adverse events[875,878-880] when receiving full dose topotecan.

For eGFR 30 – 44 mL/min/1.73 m^2, a dose reduction of 50% is recommended due to significantly altered and variable pharmacokinetics (reduced CL, potential increased systemic exposure)[872-875,877-879] and an increased risk of adverse events with declining kidney function.[874,875,879,880] There is a lack of definitive evidence for the impact of dose adjustments on therapeutic efficacy in this cohort, however one

study in patients receiving a dose reduction of 50% when eGFR 20 – 40 mL/min/1.73 m^2 observed comparable outcomes (overall response rates) to those previously reported in patients with normal kidney function.[874] Despite a dose reduction of 50%, occurrence of haematological toxicities is significantly increased in this group in comparison to patients with eGFR 45 – 59 mL/min/1.73 m^2.[875] Therefore, clinical consensus is to consider a clinically appropriate alternative treatment protocol in patients with either a poor performance status,[873,878,880] concomitant nephrotoxic drug exposure or extensive prior therapy (including, but not limited to, previous exposure to platinum therapy[878-880] or alkylating agents,[869,875] ≥ 2 successive protocols in the preceding 6 months,[874] or large field radiation to areas containing bone marrow[869,875,880]) as these cohorts have demonstrated reduced topotecan CL[878] and a higher incidence and severity of grade ≥ 3 adverse events[875,878-880] when receiving full dose topotecan.

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is to avoid topotecan and use a clinically appropriate alternative treatment protocol. There is limited pharmacokinetic, toxicity and efficacy data in patients with eGFR < 20 mL/min/1.73 m^2, and the variability in topotecan pharmacokinetics (CL, AUC) is expected to increase in this cohort. There is currently no substantial evidence to suggest that a dose reduction of topotecan when eGFR < 20 mL/min/1.73m^2 will reduce the risk of adverse events without compromising therapeutic efficacy.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice points

- Before applying a dose reduction of topotecan in kidney dysfunction, consider the extent of dose adjustment in pre-attenuated treatment protocols already accounting for poor performance status, concomitant nephrotoxic drug exposure or extensive prior therapy.
- The dose reduction applies to each individual dose and not to the total number of days or duration of topotecan per treatment cycle.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 55 – Topotecan dose recommendations according to kidney function

INTRAVENOUS TOPOTECAN DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**reduce by 30%** [a,b] **or** **full dose**	Consider a 30% dose reduction in patients with *either*: • a poor performance status • concomitant nephrotoxic drug exposure • extensive prior therapy[c] In all other patients, consider full dose. Increased risk of adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], fatigue).
30 – 44	**alternative protocol** **or** **reduce by 50%** [a,b]	Consider a clinically appropriate alternative treatment protocol in patients with *either*: • a poor performance status • concomitant nephrotoxic drug exposure • extensive prior therapy[c] In all other patients, consider a 50% dose reduction. Increased risk of adverse events (i.e., haematological toxicities [neutropenia, thrombocytopenia], fatigue).
15 – 29	**AVOID**	Not recommended – use a clinically appropriate alternative treatment protocol.
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

[a] Before applying a dose reduction of topotecan in kidney dysfunction, consider the extent of dose adjustment in pre-attenuated treatment protocols already accounting for poor performance status, concomitant nephrotoxic drug exposure or extensive prior therapy.
[b] The dose reduction applies to each individual dose and not to the total number of days or duration of topotecan per treatment cycle.
[c] Extensive prior therapy may include, but is not limited to, previous exposure to platinum therapy or alkylating agents, ≥ 2 successive protocols in the preceding 6 months, or large field radiation to areas containing bone marrow.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.52 Trastuzumab

RECOMMENDATION 4.52.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous or subcutaneous trastuzumab in all cancers.

Trastuzumab has a large molecular weight (~ 150 kDa) and is therefore unlikely to undergo glomerular filtration or urinary excretion.[881] Elimination is through the reticuloendothelial system.[881]

The pharmacokinetics of trastuzumab (C_{max}, AUC, CL, $t_{1/2}$) do not appear to be significantly influenced by kidney function (including when eGFR < 15 mL/min/1.73 m^2).[882-886]

There is limited published evidence regarding the effects of kidney dysfunction on the clinical outcomes of trastuzumab treatment. Case reports in patients with eGFR < 15 mL/min/1.73 m^2 requiring KRT, have observed that full dose trastuzumab maintained therapeutic efficacy and was well tolerated, with no dose-limiting or grade ≥ 3 toxicities.[810,811,882,884,887] Several retrospective studies reported a significantly higher incidence of cardiotoxic events in eGFR 15 – 29 mL/min/1.73 m^2 versus ≥ 90 mL/min/1.7 3m^2,[887,888] suggesting that patients with kidney dysfunction may be more vulnerable to developing cardiotoxicity when administered trastuzumab. Renal adverse events (i.e., AKI, hypokalaemia), although rare, have been reported with trastuzumab treatment.[253] It is unclear whether baseline kidney dysfunction influences the risk of trastuzumab-related renal adverse events.

For eGFR < 60 mL/min/1.73 m^2, clinical consensus is to administer full dose trastuzumab.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **moderate**; strength of recommendation: **conditional**.*

Table 56 – Trastuzumab dose recommendations according to kidney function

INTRAVENOUS and SUBCUTANEOUS TRASTUZUMAB DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59		
30 – 44		
15 – 29		
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.53 Trastuzumab Emtansine

RECOMMENDATION 4.53.1

We suggest *against* the use of kidney function to inform the initial dosing of intravenous trastuzumab emtansine in all cancers.

Trastuzumab emtansine is unlikely to be renally excreted as both drug components of this antibody-drug conjugate are reliant on other forms of elimination. Trastuzumab is unable to undergo glomerular filtration because of its large molecular weight (~ 150 kDa),[882] and emtansine is primarily eliminated through the faecal-biliary route (< 5% renally eliminated).[889]

The pharmacokinetics of trastuzumab emtansine (CL, V_d) do not appear to be significantly influenced by kidney function,[890,8913] although data is limited in patients with eGFR < 30 mL/min/1.73 m^2.

There is limited published evidence regarding the effects of kidney dysfunction on the clinical outcomes of trastuzumab emtansine treatment. Case reports in patients with eGFR < 15 mL/min/1.73 m^2 requiring KRT, have observed that full dose trastuzumab emtansine was well tolerated, with no grade ≥ 3 toxicities.[892,893] A significantly higher incidence of cardiotoxic events have been reported in eGFR 15 – 29 mL/min/1.73 m^2 versus ≥ 90 mL/min/1.73 m^2,[887] suggesting that patients with kidney dysfunction may be more vulnerable to developing cardiotoxicity when administered trastuzumab emtansine. Renal adverse events (i.e., hypokalaemia, proteinuria), although rare, have been reported with trastuzumab emtansine treatment.[894,895] It is unclear whether baseline kidney dysfunction influences the risk of trastuzumab emtansine-related renal adverse events.

For eGFR < 60 mL/min/1.73 m^2, clinical consensus is to administer full dose trastuzumab emtansine.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **moderate**; strength of recommendation: **conditional**.*

Table 57 – Trastuzumab emtansine dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS TRASTUZUMAB EMTANSINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.54 Venetoclax

RECOMMENDATION 4.54.1

We recommend *against* the use of kidney function to inform the initial dosing of oral venetoclax in all cancers. Kidney function may inform the monitoring of adverse events and the selection of an alternative treatment protocol.

Venetoclax and its metabolites are primarily eliminated in faeces, with < 0.1% of the administered dose excreted in the urine.[896,897] Although venetoclax is highly protein bound (> 99%), serum albumin concentration did not significantly influence venetoclax CL or V_d in a population pharmacokinetic analysis.[898] Venetoclax pharmacokinetics (CL, V_d, AUC) are independent of kidney function (eGFR ≥ 15 mL/min/1.73 m^2),[341,898,899] however data is limited where eGFR < 30 mL/min/1.73 m^2.[899]

Patients with reduced kidney function (eGFR range 50 – 80 mL/min/1.73 m^2) are at a significantly increased risk of TLS, a potentially fatal adverse event.[900,901] However, kidney dysfunction (e.g., AKI) may also present as an adverse complication of TLS itself,[113,902] caused by a complex interplay of crystal deposition in the kidneys and volume depletion.[113] Pre-existing kidney dysfunction impairs a patient's capacity to respond to electrolyte and fluid imbalances[900] and may increase the severity of renal complications from TLS,[113] although data is lacking where eGFR < 50 mL/min/1.73 m^2 as this cohort was excluded from clinical trials. There are currently no reports correlating kidney function with other venetoclax-related adverse events.

For eGFR 30 – 59 mL/min/1.73 m^2, full dose venetoclax is recommended, with intensive TLS prophylaxis and close monitoring.

For eGFR < 30 mL/min/1.73 m^2, clinical consensus is for a clinically appropriate alternative treatment protocol, given the paucity of pharmacokinetic and safety data in this cohort, with the aim to mitigate the exacerbation of kidney dysfunction from the increased likelihood of TLS development, especially in patients with additional TLS risk factors.[903] If an alternative protocol is not suitable and proceeding with venetoclax, clinical consensus is to administer full dose with intensive TLS prophylaxis and close monitoring.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

Practice point

- To minimise the risk of TLS in eGFR < 60 mL/min/1.73 m^2, adequate preventative measures[113,900,904-906] are advised (as per local institutional protocols) and include:
  - intravenous hydration
  - early administration of anti-hyperuricaemics
  - gradual dose escalation (‘ramp up’) of venetoclax
  - close laboratory and clinical monitoring for TLS.

*Evidence quality/certainty: **low**; strength of recommendation: **strong**.*

Table 58 – Venetoclax dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL VENETOCLAX DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m²)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td>full dose</td><td></td></tr>
<tr><td>45 – 59</td><td rowspan="2">full dose</td><td rowspan="2">Increased risk of TLS[a]</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td><td rowspan="2">alternative protocol
or
full dose</td><td rowspan="2">Consider a clinically appropriate alternative treatment protocol due to increased risk of TLS, especially in patients with additional TLS risk factors.

If an alternative protocol is not suitable and proceeding with venetoclax, consider full dose with intensive TLS prophylaxis[a].</td></tr>
<tr><td>< 15 (without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing</td></tr>
<tr><td colspan="3">[a] To minimise the risk of TLS, adequate preventative measures are advised (as per local institutional protocols) and include:
- intravenous hydration
- early administration of anti-hyperuricaemics,
- gradual dose escalation (ramp-up) of venetoclax
- close laboratory and clinical monitoring for TLS.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy; TLS, tumour lysis syndrome.</td></tr>
</table>

4.55 Vinblastine

RECOMMENDATION 4.55.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous vinblastine in all cancers.

Vinblastine is extensively metabolised by CYP450 enzymes in the liver to the more active desacetylvinblastine.[907] Elimination is primarily via biliary excretion,[908] with ~ 5 – 10% of the administered dose excreted in urine as unchanged drug and 5% as metabolites within 24 hours.[909] Vinblastine is highly protein bound (~ 99%), predominantly to α_1-acid glycoprotein.[910]

Although there is limited published evidence regarding the effects of kidney dysfunction on vinblastine systemic exposure and outcomes (adverse events and efficacy), clinically significant changes are not expected based on its pharmacokinetic profile.

For eGFR < 60 mL/min/1.73 m^2, clinical consensus is to administer full dose vinblastine.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **moderate**; strength of recommendation: **strong**.*

Table 59 – Vinblastine dose recommendations according to kidney function

<table>
<tr><th colspan="3">INTRAVENOUS VINBLASTINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

4.56 Vincristine

RECOMMENDATION 4.56.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous vincristine in all cancers.

Vincristine is metabolised by CYP450 enzymes in the liver and is primarily eliminated via biliary excretion,[911,912] with ~ 10% of the administered dose excreted in the urine as unchanged drug or metabolites within 24 hours.[911,913]

There is limited published evidence regarding the effects of kidney dysfunction on the pharmacokinetics and clinical outcomes of vincristine. Vincristine CL and plasma exposure were unaffected by kidney dysfunction (S_{Cr} > 185 µmol/L) in one pharmacokinetic study.[914] The incidence of dose reductions secondary to vincristine-related neuropathy were similar in patients with and without kidney dysfunction.[914] In a small study of paediatric patients with eGFR < 15 mL/min/1.73 m^2, administration of full dose vincristine for Wilms tumour did not increase the risk of severe haematological adverse events compared to reduced dosing.[361]

For eGFR < 60 mL/min/1.73 m^2, clinical consensus is to administer full dose vincristine.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **moderate**; strength of recommendation: **strong**.*

Table 60 – Vincristine dose recommendations according to kidney function

INTRAVENOUS VINCRISTINE DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59		
30 – 44		
15 – 29		
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.57 Vindesine

RECOMMENDATION 4.57.1

We recommend *against* the use of kidney function to inform the initial dosing of intravenous vindesine in all cancers.

Vindesine is metabolised by CYP450 enzymes in the liver and is primarily eliminated via biliary excretion,[915] with ~ 13% of the administered dose excreted in the urine as unchanged drug or metabolites within 24 hours.[913,915,916]

Although there is limited published evidence regarding the effects of kidney dysfunction on vindesine systemic exposure and outcomes (adverse events and efficacy), clinically significant changes are not expected based on its pharmacokinetic profile.

For eGFR < 60 mL/min/1.73 m^2, clinical consensus is to administer full dose vindesine.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **very low**; strength of recommendation: **strong***.

Table 61 – Vindesine dose recommendations according to kidney function

INTRAVENOUS VINDESINE DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59		
30 – 44		
15 – 29		
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.58 Vinflunine

RECOMMENDATION 4.58.1

We suggest the use of kidney function to inform the initial dosing of intravenous vinflunine in all cancers. Kidney function may inform the monitoring of adverse events.

Vinflunine is metabolised by CYP450 enzymes in the liver into several inactive metabolites and by multiple esterases into the active metabolite 4-O-deacetylvinflunine.[917] Elimination is primarily via biliary excretion,[917] with ~ 11% of the administered dose excreted in the urine as unchanged drug and < 3% as 4-O-deacetylvinflunine within 48 hours.[918,919]

Vinflunine total CL is dependent on kidney function,[920,921] with a 12% and 28% decrease in vinflunine CL mean values estimated for eGFR 41 – 60 mL/min/1.73 m^2 and eGFR 20 – 40 mL/min/1.73 m^2, respectively, compared to eGFR > 60 mL/min/1.73 m^2.[920] Vinflunine systemic exposure (AUC, C_{max}) increases with declining kidney function,[920,921] with vinflunine AUC correlated to the grade of neutropenia, leucopenia and fatigue.[918,921] A higher incidence of grade ≥ 3 vinflunine-related adverse events (i.e., neutropenia) has been observed in patients with declining kidney function.[921] There is limited published evidence on pharmacokinetic changes and clinical outcomes of vinflunine in patients with eGFR < 20 mL/min/1.73 m^2.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

RECOMMENDATION 4.58.2

We suggest the use of KDIGO CKD categories to guide dose adjustment and monitoring of intravenous vinflunine in kidney dysfunction.

There are no studies assessing the application of KDIGO CKD categories to guide dose adjustment of vinflunine and the monitoring for adverse events. Clinical consensus is that standardisation of kidney function categories across clinical settings reduces complexity of kidney function estimation and promotes uniformity.

Evidence quality/certainty: ***no studies****; strength of recommendation:* ***conditional****.*

RECOMMENDATION 4.58.3

We suggest an initial dose reduction of intravenous vinflunine in kidney dysfunction.

In addition to the following recommendations, close monitoring for adverse events (i.e., haematological toxicities [neutropenia, leucopenia], fatigue) is recommended when eGFR < 60 mL/min/1.73 m^2 (especially if proceeding with full dose) given the pharmacokinetic changes[920,921] and increased incidence and severity of adverse events[921] in this setting.

For eGFR 45 – 59 mL/min/1.73 m^2, clinical consensus is to administer full dose vinflunine given the absence of definitive evidence for the impact of dose reductions on survival outcomes and response rates in this setting. However, due to the increased risk of adverse events, a dose reduction from 320 mg/m^2 (full dose) to 280 mg/m^2 every three weeks may be considered when treatment intent is non-curative, patient has a poor performance status, or there is concomitant nephrotoxic drug exposure. This dose reduction is likely to achieve comparable systemic exposure (AUC, C_{max}) of vinflunine and its active metabolite, and reduce the incidence of grade ≥ 3 adverse events (i.e., haematological toxicities [neutropenia]) to that achieved with full dosing in patients with eGFR > 60 mL/min/1.73 m^2.[920,921]

For eGFR 15 – 44 mL/min/1.73 m^2, reducing the three-weekly dose from 320 mg/m^2 to 250 mg/m^2 is likely to achieve comparable systemic exposure (AUC, C_{max}) of vinflunine and its active metabolite, and reduce the incidence of grade ≥ 3 adverse

events (i.e., haematological toxicities [neutropenia]) to that achieved with full dosing in patients with eGFR > 60 mL/min/1.73 m^2.[920,921]

For eGFR < 15 mL/min/1.73 m^2 and/or in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.

*Evidence quality/certainty: **low**; strength of recommendation: **conditional**.*

Table 62 – Vinflunine dose recommendations according to kidney function

INTRAVENOUS VINFLUNINE DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m^2)	**Dose**	**Comment**
≥ 60	**full dose**	
45 – 59	**reduce dose** **or** **full dose**	Consider reducing from 320 mg/m^2 (full dose) to 280 mg/m^2 every 3 weeks in patients with *either*: • non-curative treatment intent • poor performance status • concomitant nephrotoxic drug exposure. In all other patients, consider full dose. Increased risk of adverse events (i.e., haematological toxicities [neutropenia, leucopenia], fatigue).
30 – 44	**reduce dose**	Reduce dose from 320 mg/m^2 (full dose) to 250 mg/m^2 every 3 weeks. Increased risk of adverse events (i.e., haematological toxicities [neutropenia, leucopenia], fatigue).
15 – 29		
< 15 (without KRT)	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	
KRT		

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

4.59 Vinorelbine

RECOMMENDATION 4.59.1

We recommend *against* the use of kidney function to inform the initial dosing of oral and intravenous vinorelbine in all cancers.

Vinorelbine is metabolised by CYP450 enzymes in the liver to various metabolites, including the active deacetyl-vinorelbine.[922] Elimination is primarily via biliary excretion, with 5 – 15% of the intravenous administered dose excreted in urine as unchanged drug (or < 5% for oral formulations) and < 1% as deacetyl-vinorelbine within 48 hours.[923-926]

Although kidney function (eGFR range 34 – 168 mL/min/1.73 m^2) has been identified in population pharmacokinetic models as an influential covariate on vinorelbine total CL, the effect sizes were small and not considered clinically significant.[927,928] There is limited published evidence regarding the effects of kidney dysfunction on vinorelbine systemic exposure and outcomes (adverse events and efficacy), however, clinically significant changes are not expected based on its pharmacokinetic profile.

For eGFR < 60 mL/min/1.73 m^2, clinical consensus is to administer full dose vinorelbine.

When dosing in KRT, consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology.

*Evidence quality/certainty: **low**; strength of recommendation: **strong***.

Table 63 – Vinorelbine dose recommendations according to kidney function

<table>
<tr><th colspan="3">ORAL and INTRAVENOUS VINORELBINE DOSE RECOMMENDATIONS</th></tr>
<tr><th>eGFR (mL/min/1.73 m^2)</th><th>Dose</th><th>Comment</th></tr>
<tr><td>≥ 60</td><td rowspan="5">full dose</td><td rowspan="5"></td></tr>
<tr><td>45 – 59</td></tr>
<tr><td>30 – 44</td></tr>
<tr><td>15 – 29</td></tr>
<tr><td>< 15
(without KRT)</td></tr>
<tr><td>KRT</td><td colspan="2">Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td></tr>
<tr><td colspan="3">Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.</td></tr>
</table>

Glossary

Term	Definition
Acute kidney injury (AKI)	Sudden decline in kidney function due to kidney damage that occurs within a few hours or days. Generally defined by an abrupt rise in serum creatinine and reduced urine output.
Acute tubular necrosis	A form of acute kidney injury that involves loss of entire tubule segments due to necrotic death of tubular epithelial cells (commonly due to nephrotoxic agents or ischemia).
Anaemia	A lower-than-normal number or functioning of red blood cells.
Area under the curve (AUC)	Total area under the plasma drug concentration-time curve and a representation of total drug exposure. Area under the curve is proportional to a given drug dose and inversely proportional to the drug clearance.
Body mass index (BMI)	Measure for indicating nutritional status in adults. Ranges of body mass index (BMI) are based on the influence of excess body fat on disease and death. BMI (kg/m^2) = actual body weight (kg) ÷ height^2 (m)
Body surface area (BSA)	Measured or calculated surface area of the human body. Considered to be a marker of metabolic function and often used to calculate anticancer drug doses. Although several equations exist for estimation of body surface area (BSA), the most commonly used are the Mosteller and DuBois DuBois equations. Mosteller equation[929]: BSA (m^2) = √ (height [cm] x weight [kg] ÷ 3600) DuBois DuBois equation[930]: BSA (m^2) = 0.007184 x height $(cm)^{0.725}$ x weight $(kg)^{0.425}$
Body surface area-adjusted estimated glomerular filtration rate	When body surface area (BSA) standardised eGFR (mL/min/1.73 m^2) is adjusted to an individual's actual body BSA (m^2). BSA is calculated using either Mosteller or DuBois DuBois equations. BSA-adjusted eGFR (mL/min) = eGFR (mL/min/1.73 m^2) x BSA ÷ 1.73
CAR T-cell	Chimeric antigen receptor T lymphocyte cell
Chronic kidney disease (CKD)	Reduced glomerular filtration rate (GFR < 60 mL/min/1.73 m^2) or a marker of kidney damage (i.e., albuminuria, history of kidney transplantation, structural abnormalities) present for > 3 months.[27]

Chronic Kidney Disease – Epidemiology Collaboration equation (to calculate $eGFR_{CKD-EPI}$)	An equation used to estimate glomerular filtration (eGFR) rate using either serum creatinine (S_{Cr}) or cystatin C (S_{Cys}).
	
	In females using CKD-EPI 2009 equation with S_{Cr},
	if $S_{Cr} \leq 62$ µmol/L:
	eGFR (mL/min/1.73 m^2) = $144 \times [S_{Cr} \times 0.0113/0.7]^{-0.329} \times [0.993]^{age}$
	if $S_{Cr} > 62$ µmol/L:
	eGFR (mL/min/1.73 m^2) = $144 \times [S_{Cr} \times 0.0113/0.7]^{-1.209} \times [0.993]^{age}$
	
	In males using CKD-EPI 2009 equation with S_{Cr},
	if $S_{Cr} \leq 80$ µmol/L:
	eGFR (mL/min/1.73 m^2) = $141 \times [S_{Cr} \times 0.0113/0.9]^{-0.411} \times [0.993]^{age}$
	if $S_{Cr} > 80$ µmol/L:
	eGFR (mL/min/1.73 m^2) = $141 \times [S_{Cr} \times 0.0113/0.9]^{-1.209} \times [0.993]^{age}$
	*race coefficient for African Americans [x 1.159] is optional
	
	Using the CKD-EPI 2012 equation with S_{Cys},
	if $S_{Cys} \leq 0.8$ mg/L:
	eGFR (mL/min/1.73 m^2) = $133 \times [S_{Cys}/0.8]^{-0.499} \times [0.996]^{age} \times$ [0.932 if female]
	if $S_{Cys} > 8$ mg/L:
	eGFR (mL/min/1.73 m^2) = $133 \times [S_{Cys}/0.8]^{-1.328} \times [0.996]^{age} \times$ [0.932 if female]

Clearance (CL)	The volume of blood cleared of a drug per unit time (e.g., L/hour) into the urine, gut contents, expired air, sweat, etc. Clearance can be referred as per an organ (kidney = *renal clearance*) or as total body clearance (sum of all the different clearance processes for a given drug). *Renal clearance* is the result of glomerular filtration, active tubular secretion and reabsorption.
Cockcroft-Gault equation	An equation used to estimate creatinine clearance based on age, weight, serum creatinine (S_{Cr}), and sex. CrCl (mL/min) = ([140 – age] x weight (kg) x [0.85 if female]) ÷ (S_{Cr} (µmol/L) x 0.814)
Creatinine	Creatinine is a breakdown product of dietary meat and creatine phosphate found in skeletal muscle. Its production in the body is dependent on muscle mass.
Creatinine clearance (CrCl)	The volume of blood plasma cleared of creatinine per unit time which includes glomerular filtration rate (as the glomerulus freely filters creatinine) and tubular secretion.
24-hour creatinine clearance	Direct measurement of creatinine clearance using a 24-hour urine sample collection.
Cytochrome P450 enzyme (CYP450)	A superfamily of enzymes that modify substances (e.g., drugs) by oxidation, hydroxylation, dealkylation, or dehalogenation, thereby increasing polarity and solubility and thus facilitating excretion from the body.
Directly measured glomerular filtration rate (mGFR)	Direct measurement of an exogenous marker such as inulin, iothalamate, ^{51}Cr-EDTA, or iohexol (and expressed in mL/min)
Estimated glomerular filtration rate (eGFR)	Prediction of glomerular filtration rate using an equation and a patient's parameters (e.g., age, sex, serum creatinine)
Fractionated dose	Dividing of a dose over several consecutive days (e.g., days 1 to 5 of treatment cycle). Differs from *split* dosing where a dose might be divided across a treatment cycle with at least a week between separated doses to enable recovery (e.g., days 1, 8 and 15 of treatment cycle).
Glomerular filtration rate (GFR)	The volume of filtrate passing the glomerular filtration barrier per unit of time; a marker of excretory kidney function.
Intent of treatment	*Curative* is anticancer treatment that aims to cure the disease. *Non-curative* is anticancer treatment that aims to prolong survival.
Half-life ($t_{½}$)	The elimination half-life of a drug is a pharmacokinetic parameter that is defined as the time it takes for the concentration of the drug in the plasma or the total amount in the body to be reduced by 50%.
Kidney dysfunction	Estimated glomerular filtration rate < 60 mL/min/1.73 m^2
Kidney failure	Complete (and life-threatening) loss of kidney function, formerly known as end-stage kidney disease (eGFR < 15 mL/min/1.73 m^2 or treatment by dialysis).
Kidney replacement therapy (KRT)	Modalities of treatment that are used to replace the waste filtering functions of a normal kidney during kidney failure. Modalities include forms of dialysis, plasmapheresis, or a kidney transplant.
Leucopenia	A lower-than-normal number of white blood cells.
Maximum concentration	Known as C_{max}, it is the highest concentration of a drug in the blood or target organ after a dose is given.
Minimum concentration	Known as C_{min}, it is the lowest concentration of a drug in the blood or target organ after a dose is given.
Modification of Diet in Renal Disease Study (MDRD) equation	An equation used to estimate glomerular filtration rate (eGFR) using age, sex, serum creatinine (S_{Cr}) and race.[931] eGFR (mL/min/1.73 m^2) = 175 x [serum creatinine/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [0.742 if female] x [1.212 if African American]
Myelosuppression	Lower-than-normal production of red blood cells, white bloods, and platelets
Nephrotoxic	Injury/poison to the kidney affecting kidney function and predominantly drug-induced (nephrotoxic drugs).
Neutropenia	Lower-than-normal number of neutrophils (type of white blood cell) in the blood
Oral drug administration	Drug ingested through the mouth in liquid, tablet or capsule form and requires absorption from the gastrointestinal tract to achieve adequate systemic

	exposure.
Parenteral drug administration	Any non-oral means of administration, but generally injecting directly into the body, bypassing the skin and mucous membranes.
Pharmacodynamics	Effect of a drug on the body.
Pharmacokinetics	Effect of the body on a drug (absorption, distribution, metabolism, and excretion).
Protocol	Standardised, detailed treatment plan for anticancer drug(s) administration involving amount, sequence and timing of doses and duration/number of cycles to treat a particular cancer.
Split dose	Dividing of a dose across a treatment cycle with at least a week between separated doses to enable recovery (e.g., days 1, 8 and 15 of a treatment cycle). Differs from *fractionated* dosing where a dose is divided over several consecutive days (e.g., days 1 to 5 of treatment cycle).
Therapeutic drug monitoring (TDM)	The individualisation of dosage by maintaining plasma or blood drug concentrations within a target range.
Third space effusion	Accumulation of fluid in body cavities.
Thrombotic microangiopathy	Consists of microangiopathic haemolytic anaemia from red blood cell fragmentation, thrombocytopaenia and end-organ damage, including acute kidney injury.
Thrombocytopenia	A lower-than-normal number of blood platelets.
Tumour lysis syndrome (TLS)	Oncological emergency in which breakdown of tumour cells, either spontaneously or in response to treatment, releases intracellular contents into the circulation, resulting in hyperuricaemia, hyperkalaemia, hyperphosphatemia, secondary hypocalcaemia, metabolic acidosis, and acute kidney injury. Malignancies with higher tumour burden and rapid cell growth rates are most associated with tumour lysis syndrome.
Volume of distribution (V_d)	A pharmacokinetic parameter that represents the drug's ability to either remain in the plasma or redistribute to other tissue compartments.

Acronyms

Acronyms	
ADDIKD	International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction
AIC	5-aminoimidazole-4-carboxamide
AKI	Acute kidney injury
AML	Acute myeloid leukaemia
Ara-CTP	Aracytidine-5'-triphosphate
Ara-U	Uracil arabinoside
AUC	Area under the curve
BSA	Body surface area
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
CL	Clearance
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum systemic concentration
C_{min}	Minimum systemic concentration
CNS	Central nervous system
^{51}Cr-EDTA	Radioactive chromium complex with ethylene diamine tetracetic acid
CrCl	Creatinine clearance
CYP450	Cytochrome P450 enzymes
dFdCDP	Gemcitabine diphosphate
dFdCTP	Gemcitabine triphosphate
5'-DFUR	5'-deoxy-5-fluorouridine

DPD	Dihydropyrimidine dehydrogenase; (*DPDY* - DPD gene)
dFdU	2, 2'-difluorodeoxyuridine
dFdUDP	2, 2'-difluorodeoxyuridine diphosphate
dFdUTP	2, 2'-difluorodeoxyuridine triphosphate
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
$eGFR_{CKD-EPI}$	eGFR calculated using Chronic Kidney Disease – Epidemiology Collaboration 2009 equation using serum creatinine
eGFR ($CKD\text{-}EPI_{cys}$)	eGFR calculated using Chronic Kidney Disease – Epidemiology Collaboration 2012 equation using serum cystatin C
e.g.,	For example
EMA	European Medicines Agency
F-ara-A	9-β-D-arabinofuranosyl-2-fluoroadenine
F-ara-ATP	9-β-D-arabinofuranosyl-2-fluoroadenine triphosphate
FDA	USA Food and Drug Administration
5-FU	5-fluorouracil
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GRADEpro GDT	GRADEpro Guideline Development Tool
hr	Hour(s)
HUS	Haemolytic uraemic syndrome
i.e.,	That is
IGHV	Immunoglobulin heavy-chain variable region
IU	International units
kDa	Kilodalton(s)
KDIGO	Kidney Disease: Improving Global Outcomes
kg	kilogram

KRT	Kidney replacement therapy
L	Litre(s)
m^2	Square metre(s)
MDRD	Modification of Diet in Renal Disease Study equation
mg	Milligram(s)
mGFR	Measured glomerular filtration rate
min	Minute(s)
mL	Millilitre(s)
MTIC	3-methyl(triazen-1-yl) imidazole-4-carboxamide
nab-paclitaxel	Nanoparticle albumin-bound paclitaxel
PAAM	Phenylacetic acid mustard
pH	Power of hydrogen (scale measuring acid/alkaline nature of solution)
PI/ECO	Patient/problem, Intervention/Exposure, Comparison or control, Outcome framework
RCC	Renal cell carcinoma
S_{Cys}	Serum cystatin C
S_{Cr}	Serum creatinine
$t_{½}$	Half-life
^{99m}Tc-DTPA	TC-diethylenetriaminepentaacetic acid
TDM	Therapeutic drug monitoring
TEPA	Triethylenephosphoramide
TLS	Tumour lysis syndrome
TPMT	Thiopurine methyltransferase
µmol	Micromole(s)
V_d	Volume of distribution

VEGF-TKI	Vascular endothelial growth factor receptor–tyrosine kinase inhibitor

Appendix 1 – Key clinical questions

Key clinical questions PI/ECO (Patient/problem, Intervention/Exposure, Comparison or control, Outcome) framework with critical (C) and important (I) outcomes

1. Should this drug be grouped as > 30% renally eliminated[a] and/or demonstrating unwanted pharmacodynamics effects in kidney dysfunction?

Population	Intervention	Comparator	Outcomes
Adult patients receiving anticancer drug	Pharmacokinetic analysis of drug (and its active metabolites) metabolism and excretion	No comparator	• >30% renal elimination of drug or its active metabolites (C) • Pharmacokinetic differences between patients with normal and impaired kidney function (C) • Incidence of nephrotoxicity (C)
Adult patients receiving anticancer drug	Observation of side effects post drug administration in patients with kidney dysfunction	Observation of side effects post drug administration in patients with normal kidney function	• Incidence of any side effects in patients with kidney dysfunction (C)

2. Will dose adjustments for this drug in a) mild, b) moderate and c) severe kidney dysfunction result in reduced toxicity without compromising therapeutic efficacy (survival, response)?

Population	Intervention	Comparator	Outcomes
Adult patients receiving anticancer drug who have impaired kidney function	Full dose administered in kidney dysfunction	Dose reduction in kidney dysfunction	• Survival outcomes (C) • Incidence of hospital admissions (C) • Reduced treatment response (C) • Incidence of grade 3-4 toxicities[932] (C) • Incidence of treatment cessation (C) • Incidence of subsequent cycle dose modification/delay (C) • Changed pharmacokinetics (C) • Feasibility in adjusting ongoing doses during the cycle (I)

3. Should the dose adjustments for this drug be indexed to the severity of kidney dysfunction as classified by Kidney Disease Improving Global Outcomes Practice Guidelines?[27,115]

Population	Intervention	Comparator	Outcomes
Adult patients receiving anticancer drug who have impaired kidney function	Dose reduction based on KDIGO classification of kidney function	Dose reduction based on non-KDIGO classification of kidney function	• Practicality of the method for measuring renal function (I) • Feasibility of adjusting ongoing doses during the cycle (I)

[a] As per the US Food and Drug Administration (FDA) criteria for renally cleared drug as > 30% the dose being eliminated unchanged in the urine[95]

Appendix 2 – Literature search strategy

Preliminary database searching was carried out to validate and refine the clinical questions, as well as determining the quantity of literature available and the relevance of the outcomes. Databases PubMed, Cochrane Library and EMBASE were used, along with grey literature and registered drug product information. The steps performed:

1. The individual search components (population, intervention, control, outcome, methodology and limits) were specified.

2. Search terms for each concept were identified. For each key word, synonyms, abbreviations, related terms, differences in spelling, old and new terminology, generic names, and lay and medical terminology were considered. Index terms unique to each database were identified – e.g., Medical Subject Headings (MeSH) terms for Medline and PubMed, and EMTREE terms for EMBASE. When there was no adequate index term a combination of text words was used to cover this concept.

3. Search terms within each component (e.g., intervention) were combined using the Boolean operator 'OR'.

4. Component sets were combined using the Boolean operator 'AND' (i.e., search terms for population AND search terms for intervention AND search terms for comparison AND search terms for outcomes AND search terms for methodology and limits).

The grey literature and registered drug product information searches involved screening references of included studies, Google /Google Scholar, government reports, and regulatory drug submissions.

Database search terms included:

((((((((((kidney[MeSH Terms]) OR renal[Title]) OR kidney[Title]) OR nephrot*[Title]))) AND (((((((acute kidney injury[MeSH Terms]) OR dysfunction[Title/Abstract]) OR impairment[Title/Abstract]) OR insufficien*[Title/Abstract]) OR clearance[Title/Abstract]) OR function[Title/Abstract]))) AND ((((((pharmacokinetic[MeSH Terms]) OR pharmacolog[Title/Abstract]) OR dosing[Title/Abstract]) OR dose adjustment[Title/Abstract]) OR dose modification[Title/Abstract]) or dose reduction[Title/Abstract]))) AND (((((((*drug name being searched* [MeSH Terms])

Grey literature search terms included:

"renal impairment" OR "renal dysfunction" OR "kidney impairment" OR "kidney dysfunction" AND "*drug name being searched*"

Once identified, records were screened and assessed for their eligibility by two independent reviewers.

Inclusion criteria:

- Published in a peer reviewed journal/conference abstract OR drug regulatory/government report.
- Any time period for publication.

Specific inclusion criteria for

a. Clinical Question 1:
    - Describes the metabolism and excretion of the specific anticancer drug,

    or

    - Reports on degree of toxicity experienced with the specific anticancer drug during kidney dysfunction
b. Clinical Question 2:
    - Describes outcomes (toxicity and/or efficacy) in kidney dysfunction for the specific anticancer drug or its drug class
    - Describes a dose reduction for the specific anticancer drug or its drug class
c. Clinical Question 3:
    - Describes how kidney function was measured in the study
    - Describes dose reductions based on kidney function criteria

Exclusion criteria includes:

- Non-human study subjects (laboratory, animal)

Appendix 3 – Summary of evidence process

ADDIKD's guideline team constructed an evidence profile by drug and clinical question. Each included study was summarised for its characteristics (design, participants, and interventions), outcomes and results in preparation for appraisal into an evidence profile. The GRADE approach was applied to assess the certainty of the evidence for each outcome in these evidence profiles (as per National Health and Medical Research Council's [NHMRC] standards on evaluating evidence).[34,37]

The quality of the records within the evidence profile was assessed using the following factors:

1. Study design
    - Classification of study design will be determined using the Cochrane Collaboration's Study Design Guide (http://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/Study_design_guide2013.pdf)[933]
    - Randomised trials provide high certainty in the evidence. Non-randomised/observational studies will provide low certainty of the evidence.
2. Risk of bias
    - Assessment of bias using the GRADE approach examines the limitations of design and conduct of each study (see *Table 64*).
    - If the bias is not plausible, doubts over the quality and limitations of the study need to be considered. Serious limitations will downgrade the certainty of the evidence by one level, whilst very serious limitations will downgrade the level by two.
3. Indirectness
    - Significant differences in the study populations, interventions and/or outcomes from the available evidence compared to those directly targeted in the guideline would downgrade the evidence certainty level. In order words, it is the inability to directly compare effects of the studies to answer the clinical questions posed in the guideline.
4. Inconsistency
    - Large unexplained heterogeneity of study results that cannot be attributed to differences in study methods, populations, interventions, or outcomes will lower the quality of the evidence.
    - Minimal or no overlap of confidence intervals between studies, differences in direction/magnitude of effects, and/or a high I^2

(quantifies proportion of variation in point estimates) suggest large variation between studies (more heterogeneity).

- If only one study is being assessed, then consistency is not applicable.
- The magnitude of the inconsistency will determine if the evidence certainty level is downgraded by one or two levels.

5. Imprecision
    - If the sample size is small and/or confidence intervals are wide enough to include appreciable benefit and harm, then results may be imprecise resulting in the evidence certainty level being downgraded by one or two levels.
6. Publication bias
    - Systematic underestimation or overestimation of outcomes via selective reporting of results can reduce the quality of evidence.
    - If publication bias is strongly suspected the evidence certainty level may be downgraded by one level.
7. Magnitude of the effect
    - Observation of a large (relative risk > 2 or < 0.5) or very large effect (relative risk > 5 or < 0.5) and consistent magnitude of effects, increases the confidence in the evidence.
    - The certainty level of the evidence in non-randomised studies, not already downgraded for any other reason, may increase by one or two levels.
8. Dose-response gradient
    - Presence of a dose-response gradient may upgrade the certainty of the evidence for non-randomised studies by one level.
    - Upgrades in the level of certainty will only be considered in studies not reduced in their certainty for other reasons.
9. Direction of plausible bias
    - Occasionally all plausible confounders may be underestimating the true effect of non-randomised studies, suggesting an increase in the certainty level of the evidence by one level.
    - Upgrades in the level of certainty will only be considered in studies not reduced in their certainty for other reasons.

The overall certainty in the evidence was the combined rating of the levels across all categories for critical and important outcomes (listed in *Appendix 1 – Key clinical questions)*. If the certainty differs across critical outcomes, the lowest certainty level becomes the overall certainty of the evidence. This process was summarised using an evidence profile.

The summary of findings table provided a concise outline of the key information around studies included in each outcome (number of patients, size effect, certainty of evidence and importance of outcome) and facilitated decision making on recommendation development in the next stage.

Table 64 – Limitations that lead to bias as per study design and downgrading of evidence certainty

Randomised trials	Non-randomised studies
• Selection bias - lack of allocation concealment, random sequence generation not conducted. • Performance bias/detection bias - lack of blinding. • Attrition bias - incomplete accounting of patients and outcome events. • Reporting bias - selective outcome reporting • Other bias – Stopping trial early for benefit – Use of unvalidated outcome measures – Carryover effects in crossover trial – Recruitment bias in cluster randomised trials	• Failure to develop and apply appropriate eligibility criteria (inclusion of control population). • Flawed measurement of both exposure and outcome. • Failure to adequately control confounding. • Incomplete or inadequately short follow-up.

Appendix 4 – Evidence-to-decision framework

At least two members of the *Content Development Group* independently reviewed the summary of evidence assessments (evidence profile and summary of findings tables) for each clinical question per anticancer drug, to aid in drafting recommendations with evidence-to-decision framework using GRADEpro GDT.[38] Drafted recommendations were further refined at small panel discussions (including members of the *Content Development Group* and invited experts).

The strength and direction of a recommendation was determined by the:

- Certainty in the evidence (higher level of certainty in the evidence is more likely to merit a strong recommendation).
- Balance between the benefits and harms specifically considering the importance of the outcomes and the magnitude of the effects. Larger differences between the effects will warrant more certainty in a strong recommendation, whilst marginal differences will likely incur a conditional/weak recommendation.
- Values and preferences of individuals undergoing intervention or the experiences of the Content Development Group / external stakeholders in dealing with these patients. Greater variability/uncertainty about values and preferences in these patients will warrant a weaker/conditional recommendation and may infer that a single recommendation would not uniformly fit across all patients.
- Resources and cost effectiveness which may also consider quality of life and indirect costs. The more resource intensive an intervention is, the more likely it will lead to a weak/conditional recommendation.

Other factors that need to be considered in the evidence-to-decision framework are a recommendation's impact on:

- Equity – does the intervention disadvantage any groups of patients i.e., patients from culturally and linguistically diverse backgrounds?
- Acceptability – is the intervention likely be easily implemented by stakeholders and accepted by patients?
- Feasibility – what barriers exist to for stakeholders to implement the intervention?

Appendix 5 – Nephrotoxic anticancer drugs

Anticancer drugs demonstrating nephrotoxic potential[934-936] include (but are not limited to):

- Aflibercept
- Arsenic trioxide
- Axitinib
- Azacitidine
- Bevacizumab
- Bleomycin
- Bortezomib
- Carboplatin
- Carfilzomib
- Cisplatin
- Clofarabine
- Crizotinib
- Cyclophosphamide
- Daunorubicin
- Doxorubicin
- Everolimus
- Gemcitabine
- Ifosfamide
- Interferons
- Interleukin-2
- Ipilimumab
- Lenalidomide
- Methotrexate
- Mitomycin
- Nivolumab
- Oxaliplatin
- Pazopanib
- Pembrolizumab
- Pemetrexed
- Regorafenib
- Sorafenib
- Sunitinib
- Vemurafenib

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