Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction:

Anticancer drug specific recommendations on dose adjustment in kidney dysfunction

Background

Kidney dysfunction, a common dosing consideration in patients with cancer[1] may alter the pharmacokinetics and pharmacodynamics of renally eliminated anticancer drugs.[2] Available anticancer drug dosing recommendations in kidney dysfunction are often empirical, lacking applicability to globally accepted kidney dysfunction classifications, and are inconsistent with the magnitude of dose reductions between different protocols with similar treatment intent.[3] The guideline aims to provide standardised, evidence-based, clinically relevant and practical recommendations on dose adjustment for anticancer drugs in kidney dysfunction.

Method

An expert international multidisciplinary working group was established to develop the *International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction* (ADDIKD).[4] The best practice framework for guideline development was utilised (Figure 1).[5] An extensive primary evidence literature search (PubMed, Cochrane Library and EMBASE databases) with grey literature and registered drug product information, aimed to identify renal elimination and nephrotoxic potential of individual anticancer drugs. Literature was summarised according to three clinical questions:

1. **Should renal elimination vs. non-renal elimination be used for direct dosing?**
2. **Should full dose vs. reduced dose be used for patients with kidney dysfunction?**
3. **Should Kidney Disease Improving Global Outcomes (KDIGO)[6] chronic kidney dysfunction categories vs. other categories be used in dose adjustment for kidney dysfunction?**

Figure 1: A summary of the guideline development process (adapted from the GRADE handbook[7])

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[7] was used to critically appraise the quality and strength of the evidence and formulate recommendations for the three clinical questions. Recommendations were refined in small panel discussions (involving working party members and expert clinicians) prior to anonymous voting by the entire working group to achieve consensus.

Results

Review of 2263 articles and 177 registered product information monographs enabled 59 drug specific GRADE assessments. The working group applied the national consensus recommendations[4] and KDIGO categories to formulate 127 evidence-based and clinical consensus dosing recommendations for the 59 drugs (with 'quick reference' dosing tables (Figure 2)). A traffic light system was applied to alert clinicians to caution around levels of kidney function within the 'quick reference' dosing tables. The first edition of ADDIKD will undergo an extensive external consultation until the end of 2021.

Conclusion

With its target audience of junior cancer team members, the ADDIKD guideline provides an internationally standardised approach to dose adjustment in kidney dysfunction, aiming to optimise safer and efficacious delivery of cancer treatments. The first edition of the ADDIKD guideline, and its implementation into eviQ protocols, will progress its international dissemination and endorsement as a clinical benchmark.

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Figure 2. Example of the drug dosing table for high-dose cytarabine

HIGH-DOSE (> 1000 mg/m²) CYTARABAINE DOSING RECOMMENDATION [a]		
eGFR (mL/min/1.73 m²)	**Dose**	**Comment**
≥ 60	**Full dose**	
45-59	**Alternative regimen or reduce by 50%[b]**	Consider alternative regimen in curative intent. Avoid further dose reduction if using an age-adjusted dose in treatment regimen. Increased risk of adverse events (e.g. neurological toxicity)
30-44		
15-29	**AVOID**	Not recommended - use an alternative regimen
< 15 (without kidney replacement therapy)		
Kidney replacement therapy	A multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology is recommended for the management of dosing	

[a] For bone marrow transplantation conditioning protocols, please consult the transplant team if the patient has kidney dysfunction and is requiring this drug as part of their regimen. The recommended 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 cytarabine per treatment cycle.

References:

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