Burkitt lymphoma IVAC (iFOSFamide etoposide cytarabine) SUPERSEDED

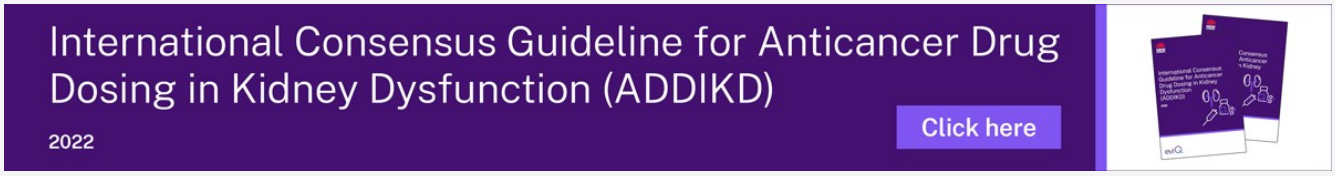
ID: 549 v.8 **Superseded** Essential Medicine List

This protocol has been superseded as a superior alternative is available for use in clinical practice. ID 3725 Burkitt lymphoma R-IVAC is the more commonly used regimen.

Patients with lymphoma should be considered for inclusion into clinical trials. Link to ALLG website, ANZCTR website and Lymphoma Australia website.

This protocol is based on limited evidence; refer to the evidence section of this protocol for more information.

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.



Related pages:

- Burkitt lymphoma dmCODOX-M/IVAC overview SUPERSEDED
- Burkitt lymphoma dose modified CODOX-M (CYCLOPHOSPHamide vinCRISTine DOXOrubicin methotrexate) SUPERSEDED

Treatment schedule - Overview

Drug	Dose	Route	Day
Cytarabine (Ara-C)	2,000 mg/m^2 TWICE a day (12 hours apart)*	IV infusion	1 and 2
Etoposide **	60 mg/m^2	IV infusion	1 to 5
Mesna	360 mg/m^2	IV infusion	1
iFOSFamide	1,500 mg/m^2 *	IV infusion	1 to 5
Mesna	1,500 mg/m^2	IV infusion	1 to 5
Methotrexate	12 mg	Intrathecal	5
Calcium folinate (Leucovorin) ***	15 mg	PO	6
Filgrastim	5 micrograms/kg	Subcut	7 and continue daily until neutrophil recovery

* Please see "Dose modifications" for cytarabine and ifosfamide in patients older than 65 years.

** Etopophos (etoposide phosphate) 113.6 mg is equivalent to etoposide 100 mg. Doses in this protocol are expressed as etoposide.

*** Administered 24 hours after intrathecal methotrexate

IVAC to commence on the first day after CODOX-M that ANC is greater than 1.0 x10^9/L and platelets are greater than 75 x10^9/L

Link to the International Non-Hodgkin Lymphoma International Prognostic Index (IPI)

Low risk disease	THREE cycles of dmCODOX-M[1]
High risk disease	Alternating dmCODOX-M / IVAC *TWICE* (i.e. dmCODOX-M / IVAC / dmCODOX-M / IVAC)[1]
Proven CNS disease	Additional intrathecal cytarabine 70 mg administered on Day 7 and 9 with FIRST cycle of IVAC only. **Note:** This is in **addition** to intrathecal methotrexate given in Day 5 as part of the IVAC protocol

Patients are considered **Low Risk** if they have *at least 3* of the following international prognostic index (IPI) factors:

- normal LDH
- Ann Arbor stage I to II
- WHO performance status 0 to 1
- number of extra nodal sites less than or equal to 1

All other patients are considered **High Risk**

Notes:

- Patients presenting with CNS disease are to receive **additional** intrathecal therapy with cytarabine on Days 7 and 9 with the first cycle of IVAC only.
- The dosing schedule of mesna in this protocol differs from the regimen reported in the LY10 trial, and was selected by the Haematology reference committee to reflect clinical practice.

Drug status: All drugs in this protocol are on the PBS general schedule

Filgrastim: (PBS authority)

Cost: ~ $3,310

Treatment schedule - Detail

The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

Day 1		
Cytarabine (Ara-C)	2,000 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 3 hours TWICE a day (12 hours apart) for a total of 4 doses *
Etoposide	60 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes
Mesna	360 mg/m^2 (IV infusion)	in 250 mL sodium chloride 0.9% over 15 minutes as a loading dose 60 minutes before first dose of ifosfamide
iFOSFamide	1,500 mg/m^2 (IV infusion)	in 500 mL to 1000 mL sodium chloride 0.9% over 2 hours *
Mesna	1,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 24 hours

Day 2		
Cytarabine (Ara-C)	2,000 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 3 hours TWICE a day (12 hours apart) for a total of 4 doses *
Etoposide	60 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes
iFOSFamide	1,500 mg/m^2 (IV infusion)	in 500 mL to 1000 mL sodium chloride 0.9% over 2

Day 2		
		hours *
Mesna	1,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 24 hours
Day 3 and 4		
Etoposide	60 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes
iFOSFamide	1,500 mg/m^2 (IV infusion)	in 500 mL to 1000 mL sodium chloride 0.9% over 2 hours *
Mesna	1,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 24 hours
Day 5		
Etoposide	60 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes
iFOSFamide	1,500 mg/m^2 (IV infusion)	in 500 mL to 1000 mL sodium chloride 0.9% over 2 hours *
Mesna	1,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 24 hours
Methotrexate	12 mg (Intrathecal)	adhere to local institution intrathecal policy
Day 6		
Calcium folinate (Leucovorin)	15 mg (PO)	once only 24 hours after intrathecal methotrexate
Day 7		
Filgrastim	5 micrograms/kg (Subcut)	inject subcutaneously ONCE a day starting on day 7 and continue until ANC greater than 1.0 x 10^9/L

* Please see "Dose modifications" for cytarabine and ifosfamide in patients older than 65 years.

IVAC to commence on the first day after CODOX-M that ANC is greater than 1.0 x10^9/L and platelets are greater than 75 x10^9/L

Link to the International Non-Hodgkin Lymphoma International Prognostic Index (IPI)

Low risk disease	THREE cycles of dmCODOX-M[1]
High risk disease	Alternating dmCODOX-M / IVAC *TWICE* (i.e. dmCODOX-M / IVAC / dmCODOX-M / IVAC)[1]
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Indications and patient population

- Burkitt lymphoma in adults 65 years of age or younger
  - Patients older than 65 years require specific dose reductions (refer to 'Dose modifications')

Clinical information

Venous access	Central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection
Hypersensitivity/infusion related reaction	High risk with etoposide. Read more about Hypersensitivity reaction

Antiemetics for multi-day protocols	Antiemetic therapy should be administered throughout the duration of the chemotherapy protocol and to cover delayed nausea. The acute and delayed emetic risk of multi-day chemotherapy protocols will overlap depending on the individual drugs and their sequence of administration. More or less antiemetic cover may be required. Ensure that patients also have sufficient antiemetics for breakthrough emesis: Metoclopramide 10 mg three times a day when necessary (maximum of 30 mg/24 hours, up to 5 days) OR Prochlorperazine 10 mg PO every 6 hours when necessary. Read more about preventing anti-cancer therapy induced nausea and vomiting
Ifosfamide-induced encephalopathy	May occur in patients treated with high dose ifosfamide (~ 5 to 8 g/m^2). Assess neurological function prior to each ifosfamide dose. Read more about ifosfamide-induced encephalopathy Link to ifosfamide-induced encephalopathy assessment chart
Haemorrhagic cystitis associated with high dose chemotherapy	Hydration regimen pre high dose cyclophosphamide or ifosfamide (as per local guidelines). There is limited evidence and no consensus regarding hydration regimens and mesna dose, route or timing of administration. Read more about haemorrhagic cystitis
Cytarabine-induced neurotoxicity	This may occur in patients treated with high-dose cytarabine. Assess cerebellar function prior to each cytarabine dose. Note: an increased risk of cytarabine-induced neurotoxicity has been associated with kidney dysfunction. Read more about neurotoxicity associated with high-dose cytarabine and access the cytarabine cerebellar neurotoxicity assessment chart
Ocular toxicities	Administer corticosteroid eye drops to minimise corneal toxicity from high dose cytarabine. Commence on the day of first dose of cytarabine and continue for at least 72 hours after completion of final cytarabine dose. Read more about ocular toxicities associated with high dose cytarabine
Cytarabine syndrome	Treatment with cytarabine may cause a "cytarabine syndrome" characterised by flu-like symptoms, skin rash and occasionally chest pain.
Etoposide conversion factor	Note: Etopophos (etoposide phosphate) 113.6 mg is equivalent to etoposide 100 mg. Doses in this protocol are expressed as etoposide.
Central nervous system (CNS) prophylaxis	Consider CNS relapse assessment in patients with high grade lymphoma. Read more about CNS prophylaxis in diffuse large cell lymphoma
Tumour lysis risk	Patients are at high risk of developing tumour lysis syndrome, prophylaxis is recommended. Read more about the prevention and management of tumour lysis syndrome.
Mesna dosing and administration	There is evidence supporting variations in mesna doses and administration timings, with no clear evidence that one particular regimen is superior to another. The eviQ mesna recommendations may be based upon the individual trial/study or reference committee consensus and provide guidance on one safe way to administer the protocol. Individual institutional policy may vary and should be evidence-based. Read more about haemorrhagic cystitis
Pneumocystis jirovecii pneumonia (PJP) prophylaxis	PJP prophylaxis is recommended. Myelosuppression may be exacerbated if trimethoprim/sulfamethoxazole is used in combination with methotrexate. Read about prophylaxis of pneumocystis jirovecii (carinii) in cancer patients
Antiviral prophylaxis	Antiviral prophylaxis is recommended. Read more about antiviral prophylaxis drugs and doses
Antifungal prophylaxis	Antifungal prophylaxis is recommended. Read more about antifungal prophylaxis drugs and doses.
Biosimilar drug	Read more about biosimilar drugs on the Biosimilar Awareness Initiative page

Growth factor support	G-CSF (short or long-acting) is available on the PBS for chemotherapy induced neutropenia depending on clinical indication and/or febrile neutropenia risk. Access the PBS website
Blood tests	FBC, EUC, eGFR, LFTs and LDH at baseline, and prior to each cycle and as clinically indicated.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is recommended prior to initiation of treatment. Prophylaxis should be determined according to individual institutional policy. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.
Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

Note: All dose reductions are calculated as a percentage of the starting dose

Haematological toxicity
Next cycle to be given when ANC is 1.0 x 10^9/L or greater and platelets are greater than 75 x 10^9/L

Renal impairment	
Creatinine clearance (mL/min)	
less than 30	Reduce ifosfamide by 25%
No dose modifications required for cytarabine. However, increased risk of neurotoxicity has been associated with high dose	

Renal impairment
cytarabine when creatinine clearance is less than 60 mL/min.

Hepatic impairment	
Bilirubin (micromol/ L)	
greater than 34	Reduce cytarabine by 50%

Age older than 65 years			
Patients older than 65 years of age are to receive reduced doses of cytarabine, ifosfamide and mesna as below:[2]			
Drug	**Dose**	**Route**	**Days**
Cytarabine	1000 mg/m^2	IV infusion	1 and 2
Ifosfamide	1000 mg/m^2	IV infusion	1 to 5
Mesna	1000 mg/m^2 *	IV infusion	1 to 5
** Loading dose of mesna on day 1 remains unchanged.*			

Interactions

Drug interactions in eviQ protocols are under review and being updated to align with current literature. Further site-wide updates and changes will occur in due course. References & Disclaimer

The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*
- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

Cytarabine		
	Interaction	**Clinical management**
Cytidine deaminase (CDA) inhibitors (e.g. cedazuridine)	Potential increased effect/toxicity of cytarabine due to reduced clearance	Avoid combination or monitor for increased cytarabine effect/toxicity

Etoposide and Etoposide Phosphate		
	Interaction	**Clinical management**
CYP3A4 and P-gp inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, ciclosporin etc.)	Increased toxicity of etoposide possible due to reduced clearance	Avoid combination or monitor for etoposide toxicity
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of etoposide possible due to increased clearance	Avoid combination or monitor for decreased clinical response to etoposide
Glucosamine	Reduced efficacy of etoposide (due to induction of glucose-regulated stress proteins resulting in decreased expression of topoisomerase II)	Avoid combination or monitor for decreased clinical response to etoposide
Grapefruit juice	Reduced efficacy of oral etoposide possible due to possible alteration of P-gp mediated intestinal transport of etoposide	Avoid combination or monitor for decreased clinical response to etoposide

Ifosfamide		
	Interaction	**Clinical management**
Aprepitant	Increased risk of ifosfamide-induced neurotoxicity due to increased levels of active metabolites	Avoid combination or monitor closely for neurotoxicity; consider alternate antiemetic regimens
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Increased toxicity of ifosfamide possible due to increased conversion to active and toxic metabolites	Avoid combination or monitor for ifosfamide toxicity
CYP3A4 inhibitors (e.g. azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Reduced efficacy of ifosfamide possible due to decreased conversion to active metabolites	Avoid combination or monitor for decreased clinical response to ifosfamide
Suxamethonium	Potentiation of muscle relaxant effect possible	Alert the anaesthetist if a patient has been treated with ifosfamide within ten days of planned general anaesthesia
CNS depressants (including opiates, opioids, phenothiazines)	Increased risk of ifosfamide-induced neurotoxicity due to additive CNS effects	Avoid combination or monitor for excessive CNS depression/encephalopathy

Mesna
No specific or clinically significant drug interactions

General		
	Interaction	**Clinical management**
Warfarin	Anti-cancer drugs may alter the anticoagulant effect of warfarin.	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant.
Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, dabigatran	Interaction with both CYP3A4 and P-gp inhibitors /inducers. DOAC and anti-cancer drug levels may both be altered, possibly leading to loss of efficacy or toxicity (i.e. increased bleeding).	Apixaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. If treating VTE, avoid use with strong CYP3A4 and P-gp inducers. Rivaroxaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. Dabigatran: avoid combination with strong P-gp inducers and inhibitors. If concurrent use is unavoidable, monitor closely for efficacy/toxicity of both drugs.
Digoxin	Anti-cancer drugs can damage the lining of the intestine; affecting the absorption of digoxin.	Monitor digoxin serum levels; adjust digoxin dosage as appropriate.
Antiepileptics	Both altered antiepileptic and anti-cancer drug levels may occur, possibly leading to loss of efficacy or toxicity.	Where concurrent use of an enzyme-inducing antiepileptic cannot be avoided, monitor antiepileptic serum levels for toxicity, as well as seizure frequency for efficacy; adjust dosage as appropriate. Also monitor closely for efficacy of the anti-cancer therapy.
Antiplatelet agents and NSAIDs	Increased risk of bleeding due to treatment related thrombocytopenia.	Avoid or minimise combination. If combination deemed essential, (e.g. low dose aspirin for ischaemic heart disease) monitor for signs of bleeding.
Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)	Increased risk of serotonin syndrome with concurrent use of 5-HT3 receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	Avoid combination. If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia). For more information link to TGA Medicines Safety Update
Vaccines	Diminished response to vaccines and increased risk of infection with live vaccines.	Live vaccines (e.g. BCG, MMR, zoster and varicella) are contraindicated in patients on immunosuppressive therapy. Use with caution in patients on non-immunosuppressive therapy. For more information; refer to the recommended schedule of vaccination for cancer patients, as outlined in the Australian Immunisation Handbook

Administration

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual

product information monographs via the TGA website for further information.

Days 1 and 2

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Access CVAD.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- daily dipstick urinalysis to assess for haematuria
- strict fluid balance

Hydration if prescribed

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Cytarabine

Prior to administration:

Ensure corticosteroid eye drops have been administered before starting cytarabine.

Verify that cytarabine neurological assessment has been performed prior to administration of cytarabine:

- if the patient scores 0 then administer cytarabine as charted
- if the patient scores 1 or above, do not administer the cytarabine and immediately notify medical officer.

Administer cytarabine:

- via IV infusion over 2 to 3 hours:
- flush with ~50 mL of sodium chloride 0.9%.

Administer second dose of cytarabine 12 hours after first dose.

Etoposide

Administer etoposide (irritant):

- via IV infusion over 30 to 60 minutes
- rapid infusion may cause hypotension
- observe for hypersensitivity
- flush with ~ 100 mL sodium chloride 0.9%
- if using etoposide phosphate administer in ~ 50 mL sodium chloride 0.9% or glucose 5% over ~15 minutes.

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.
- for severe reactions seek medical assistance immediately and do not restart infusion.

Mesna

First dose of mesna (loading dose):

- administer via IV infusion over 15 minutes
- start 60 minutes prior to the commencement of ifosfamide (Day 1 only)

Second dose of mesna:

- via IV infusion
- over 24 hours (to commence immediately after loading dose)
- the administration of mesna causes a false positive ketonuria.

Ifosfamide infusion

Prior to administration:

- assess neurological function at baseline and prior to each ifosfamide dose
  - inpatients: 4 hourly assessments until 24 hours after ifosfamide infusion is completed
  - outpatients: advise patient/carer of the potential for neurotoxicity
    - neurological assessment tool
- perform baseline urinalysis and monitor for haematuria prior to each ifosfamide dose
  - note the administration of mesna will cause a false positive for ketonuria
- ensure patient receives at least 3 L of IV or oral fluids per day

Administer ifosfamide (irritant):

- via IV infusion over 2 hours
- flush with ~100 mL of sodium chloride 0.9%

Continue safe handling precautions until 7 days after completion of drug(s)

Days 3 and 4

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- strict fluid balance
- dipstick urinalysis to assess for haematuria prior to treatment

Hydration if prescribed

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Continue corticosteroid eye drops until 72 hours after completion of the last dose of cytarabine.

Chemotherapy - Time out

Etoposide

Administer etoposide (irritant):

- via IV infusion over 30 to 60 minutes
- rapid infusion may cause hypotension
- observe for hypersensitivity
- flush with ~ 100 mL sodium chloride 0.9%

- if using etoposide phosphate administer in ~ 50 mL sodium chloride 0.9% or glucose 5% over ~15 minutes.

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.
- for severe reactions seek medical assistance immediately and do not restart infusion.

Ifosfamide infusion

Prior to administration:

- assess neurological function at baseline and prior to each ifosfamide dose
  - inpatients: 4 hourly assessments until 24 hours after ifosfamide infusion is completed
  - outpatients: advise patient/carer of the potential for neurotoxicity
    - neurological assessment tool
- perform baseline urinalysis and monitor for haematuria prior to each ifosfamide dose
  - note the administration of mesna will cause a false positive for ketonuria
- ensure patient receives at least 3 L of IV or oral fluids per day

Administer ifosfamide (irritant):

- via IV infusion over 2 hours
- flush with ~100 mL of sodium chloride 0.9%

Mesna

- administer via IV infusion over 24 hours
- the administration of mesna causes a false positive ketonuria.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 5

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- strict fluid balance
- dipstick urinalysis to assess for haematuria prior to treatment

Hydration if prescribed

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Continue corticosteroid eye drops until 72 hours after completion of the last dose of cytarabine.

Chemotherapy - Time out

Etoposide

Administer etoposide (irritant):

- via IV infusion over 30 to 60 minutes
- rapid infusion may cause hypotension
- observe for hypersensitivity

- flush with ~ 100 mL sodium chloride 0.9%
- if using etoposide phosphate administer in ~ 50 mL sodium chloride 0.9% or glucose 5% over ~15 minutes.

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.
- for severe reactions seek medical assistance immediately and do not restart infusion.

Ifosfamide infusion

Prior to administration:

- assess neurological function at baseline and prior to each ifosfamide dose
  - inpatients: 4 hourly assessments until 24 hours after ifosfamide infusion is completed
  - outpatients: advise patient/carer of the potential for neurotoxicity
    - neurological assessment tool
- perform baseline urinalysis and monitor for haematuria prior to each ifosfamide dose
  - note the administration of mesna will cause a false positive for ketonuria
- ensure patient receives at least 3 L of IV or oral fluids per day

Administer ifosfamide (irritant):

- via IV infusion over 2 hours
- flush with ~100 mL of sodium chloride 0.9%

Mesna

- administer via IV infusion over 24 hours
- the administration of mesna causes a false positive ketonuria.

Intrathecal methotrexate

⚠ **Intrathecal methotrexate is to be administered today. The intrathecal procedure is to be done separately to the IV administration of all other cytotoxic drugs**

Read more about the procedure for intrathecal methotrexate administration.

Post intrathecal care:

Local policies and guidelines regarding bed rest post dural puncture should be adhered to. At a minimum:

- the patient should have at least 1 set of observations including:
  - vital signs and GCS
  - any abnormal neurological signs such as nausea, vomiting, chills, fever, confusion, headache or other changes in neurological status
- educate the patient to recognise and immediately report any adverse reactions including blurred vision, dizziness, pain and or headache
- observe the lumbar puncture site for any leakage or bleeding post procedure
- document the procedure including outcomes in the patients notes

Continue safe handling precautions until 7 days after completion of drug(s)

Day 6

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- strict fluid balance
- dipstick urinalysis to assess for haematuria prior to treatment

Hydration if prescribed

Calcium Folinate (Leucovorin)

- administer ONCE orally 24 hours after intrathecal methotrexate

Deaccess CVAD.

Day 7

Filgrastim

- administer filgrastim subcutaneous starting on day 7 and continuing until ANC is greater than 1 x 10^9/L

Discharge information

Calcium folinate (leucovorin)

- Calcium folinate (leucovorin) tablets with instructions to take 24 hours after intrathecal methotrexate.

Antiemetics

- Antiemetics as prescribed.

Corticosteroid eye drops

- Continue corticosteroid eye drops for at least 72 hours after completion of final cytarabine dose.

Growth factor support

- Arrangements for administration if prescribed.

Prophylaxis medications

- Prophylaxis medications (if prescribed) i.e. tumour lysis prophylaxis, PJP prophylaxis, antifungals, antivirals.

Patient information

- Ensure patient receives patient information sheet.

Side effects

The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.

Immediate (onset hours to days)	
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Bone pain	Bone pain, usually in the lower back or pelvis, associated with G-CSF.
Encephalopathy	Ifosfamide induced encephalopathy has been reported in 10 to 30% of patients receiving high dose ifosfamide. Common symptoms include confusion, ataxia, weakness, seizures, somnolence and hallucinations. Onset may be 2 to 48 hours after commencing treatment. When reversible, symptoms usually resolve within 1 to 3 days. Read more about ifosfamide-induced encephalopathy
Haemorrhagic cystitis	An inflammatory process, characterised by diffuse bladder mucosal inflammation resulting in haemorrhage. Patients are at risk following blood and marrow transplant (BMT) or treatment with cyclophosphamide, ifosfamide and/or radiation therapy. Read more about haemorrhagic cystitis
Neurotoxicity	High dose cytarabine has been associated with acute cerebellar syndrome and diffuse cerebral dysfunction. Read more about neurotoxicity associated with high dose cytarabine
Ocular toxicities	Reversible corneal toxicity (keratitis), haemorrhagic conjunctivitis, vision loss and other ocular side effects can occur with high dose cytarabine. Corticosteroid eye drops must be administered concurrently with treatment. Read more about ocular toxicities associated with cytarabine
Taste and smell alteration	Read more about taste and smell changes

Early (onset days to weeks)	
Neutropenia	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about immediate management of neutropenic fever
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Cytarabine (Ara-C) syndrome	Flu-like symptoms including fever, myalgia and malaise can occur 6 to 12 hours after cytarabine administration. Symptoms generally resolve within 24 hours of completing therapy.
Fatigue	Read more about fatigue
Nephrotoxicity	Renal dysfunction resulting from damage to the glomeruli, tubules or renal vasculature.
Oral mucositis	Erythematous and ulcerative lesions of the gastrointestinal tract (GIT). It commonly develops following chemotherapy, radiation therapy to the head, neck or oesophagus, and high dose chemotherapy followed by a blood and marrow transplant (BMT). Read more about oral mucositis
Skin rash	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about skin rash

Late (onset weeks to months)	
Alopecia	Hair loss may occur from all parts of the body. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Cognitive changes (chemo fog)	Changes in cognition characterised by memory loss, forgetfulness and feeling vague. This is also referred to as 'chemo brain' or 'chemo fog'. Read more about cognitive changes (chemo fog)

Delayed (onset months to years)	
Pulmonary toxicity	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about pulmonary toxicity associated with anti-cancer drugs

Evidence

This protocol has been superseded as a superior alternative is available for use in clinical practice. ID 3725 Burkitt lymphoma R-IVAC is the more commonly used regimen.

The dose modified (dm) CODOX-M/IVAC protocol for Burkitt Lymphoma (BL) is an iteration of the original treatment regimen described by Magrath et al in 1996.[3] The intention was to provide a dose intensive, compact, non cross-resistant regimen with effective CNS targeting. The promising results of this study were confirmed in the LY06 study which was a larger, multicentre, international phase 2 trial.[1] This regimen was refined in the LY10 trial, whereby methotrexate was dose modified to 3 g/m^2 (from 6.7 g/m^2) in order to reduce toxicity.[2] LY10 forms the basis of the current eviQ dmCODOX-M/IVAC protocol.

LY10 was a prospective, international, non-randomised phase 2 study that included 53 patients (median age 37 years; range 17 to 76 years) with newly diagnosed BL. Patients with documented CNS involvement received additional intrathecal therapy. The LY10 trial included 11 low risk and 42 high risk patients.[2]

Patients were considered 'Low Risk' if they had at least 3 of the 4 following international prognostic index (IPI) factors: normal LDH, Ann Arbor stage I to II, WHO performance status 0 to 1 and number of extra nodal sites less than or equal to 1. These patients were treated with three cycles of dmCODOX-M.[2]

All other patients were considered 'High Risk' and received alternating cycles of dmCODOX-M/IVAC twice. Seventy-six percent of the patients were able to complete the planned therapy. Severe (grade 3/4) toxicities included neutropenia (99%), neutropenic fever (80%), thrombocytopenia (86%), mucositis (47%), and neuropathy (8%). The treatment related death rate was 8%. Two year progression free survival (PFS) and overall survival (OS) rates were 64% and 67%, respectively.[2]

In recent years it has been common practise for rituximab to be added to the dmCODOX-M/IVAC regimen, though there has been no prospective randomised evaluation of the efficacy of this addition. The largest prospective study[4] utilised rituximab 375 mg/m^2 on day 1 of each dmCODOX-M and IVAC cycle. 15 patients with BL and 15 with unclassifiable lymphomas intermediate between BL and diffuse large B cell lymphoma were evaluated. This regimen was associated with acceptable toxicity and outcomes commensurate with historical dmCODOX-M/IVAC patients who were not exposed to rituximab. Several other groups have reported retrospective data on CODOX-M/IVAC based regimens combined with rituximab.[5, 6, 7] In view of this data, addition of rituximab seems reasonable, though ideal timing and dosing remains to be defined.

HIV-Associated Burkitt Lymphoma

HIV-associated Burkitt Lymphoma is a rare clinical entity outside of specialised centres. There is no consensus regarding optimum treatment regimen, and CODOX-M/IVAC is one option employed.
There is limited data regarding the use of CODOX-M/IVAC in HIV-associated Burkitt Lymphoma. Wang et al[8]reported retrospective outcomes of 14 adults with complete response rate of 63%. The AIDS Malignancy Consortium[9] reported prospective outcomes in 34 patients, using a modified regimen, and PFS at one year was 69% with OS 72%.

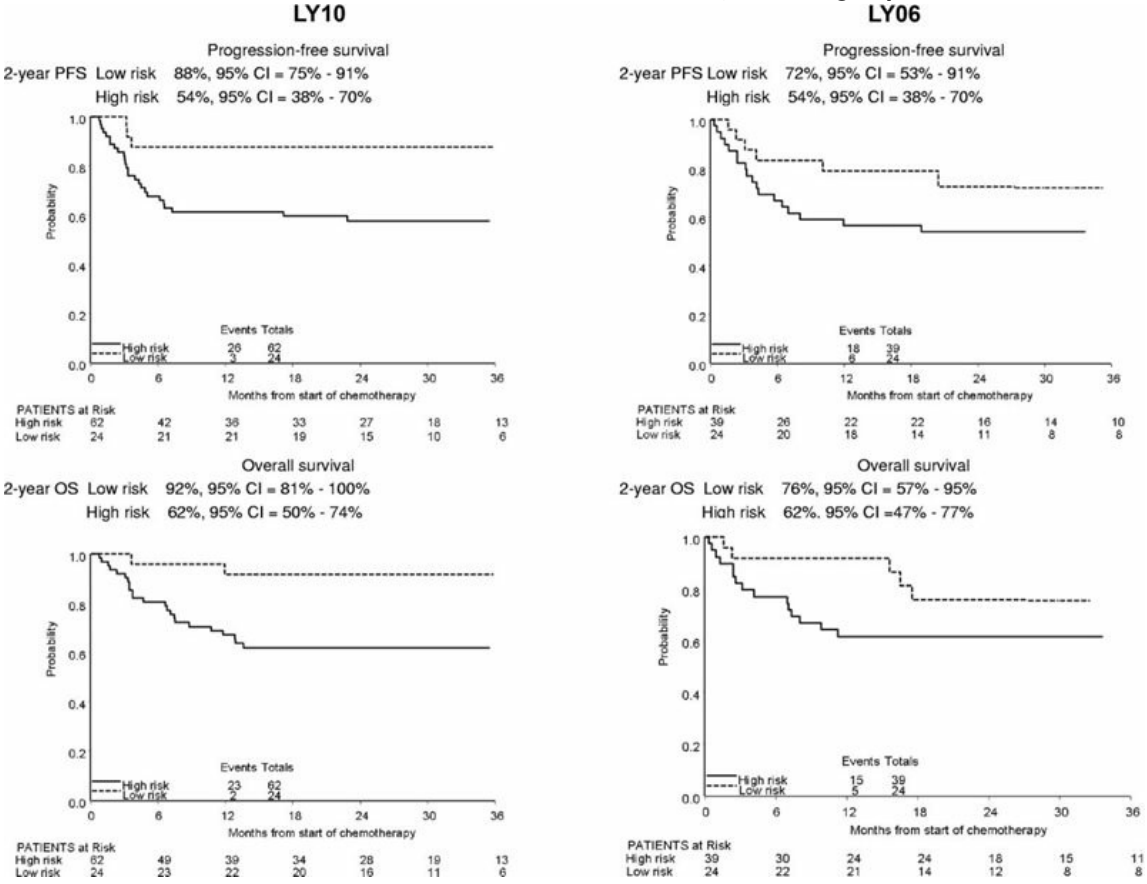
Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
Phase II	Magrath et al[3]	Yes	Yes	-

trials	LY06 trial[1]	Yes	No	Higher methotrexate dose of 6.7g / m^2 was administered
	LY10 trial[2]	Yes	Yes	-

Guidelines	Date published/revised	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
NCCN	V.5.2019	**Yes**	-	-
BCCA	May 2019	**Yes**	-	-
CCO	June 2019	**Yes**	-	-

Efficacy

Progression-free survival and overall survival in the LY06[1] and LY10[2] studies, with risk group defined as in LY10:



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Toxicity

In the LY10 study,[2] there were 9 deaths (1 low risk, 8 high risk) reported to be treatment-related, of which 5 (all high-risk patients) died within 12 weeks of starting treatment; 2 of the 9 patients were aged over 65 (66 and 67, respectively).

Table 4. Worst toxicity experienced (CTC grade) during the treatment (for 109 patients who received at least 1 cycle of protocol treatment) in dmCODOX-M/IVAC study

	Low risk, N = 33		High risk, N = 76		Total, N = 109	
	n	%	n	%	n	%
WBC						
Grade 3	1	3	0	0	1	1
Grade 4	32	97	75*	99	107	98
Neutropenic fever						
Grade 3	20	61	67	88	87	80
Neutrophil count						
Grade 3	0	0	1	1	1	1
Grade 4	32	97	75	99	107	98
Platelets						
Grade 3	5	15	1	1	6	6
Grade 4	14	42	73	96	87	80
Mucositis						
Grade 3	10	31	29	38	39	36
Grade 4	2	6	8	11	10	9
Unknown	1		0		1	
Neuropath, sensory/motor						
Grade 3	3	10	3	4	6	6
Grade 4	0	0	2	3	2	2
Unknown	3		0		3	

*One patient did not report grade 3/4 leukopenia but received only part of cycle 1 dmCODOX-M prior to disease progression.

References

1 Mead, G. M., M. R. Sydes, J. Walewski, et al. 2002. "An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study." Ann.Oncol. 13(8):1264-1274.

2 Mead, G. M., S. L. Barrans, W. Qian, et al. 2008. "A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial)." Blood 112(6):2248-2260.

3 Magrath, I., M. Adde, A. Shad, et al. 1996. "Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen." J.Clin Oncol. 14(3):925-934.

4 Corazzelli, G., F. Frigeri, F. Russo, et al. 2012. "RD-CODOX-M/IVAC with rituximab and intrathecal liposomal cytarabine in adult Burkitt lymphoma and 'unclassifiable' highly aggressive B-cell lymphoma." Br J Haematol 156(2):234-244.

5 Mohamedbhai, S. G., K. Sibson, T. Marafioti, et al. 2011. "Rituximab in combination with CODOX-M/IVAC: a retrospective analysis of 23 cases of non-HIV related B-cell non-Hodgkin lymphoma with proliferation index >95%." Br J Haematol 152(2):175-181.

6 Barnes, J. A., A. S. Lacasce, Y. Feng, et al. 2011. "Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis." Ann Oncol 22(8):1859-1864.

7 Wasterlid, T., P. N. Brown, O. Hagberg, et al. 2013. "Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group." Ann Oncol 24(7):1879-1886.

8 Wang, E. S., D. J. Straus, J. Teruya-Feldstein, et al. 2003. "Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma." Cancer 98(6):1196-1205.

9 Noy, A., J. Y. Lee, E. Cesarman, et al. 2015. "AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma." Blood 126(2):160-166.

History

Version 8

Date	Summary of changes

Date	Summary of changes
27/01/2022	Protocol superseded. Discussed at Haematology Reference Committee meeting 22 October 2021 - consensus to supersede due to superior alternative being available.Version number changed to v.8.
08/02/2022	PJP prophylaxis clinical information block updated.
19/07/2022	Dose modifications section: 'Age older than 65 years' updated.

Version 7

Date	Summary of changes
22/09/2020	Biosimilar drug added to clinical information. Version number changed to v.7
24/01/2022	Pulmonary toxicity added to side effects.

Version 6

Date	Summary of changes
16/04/2020	'Mesna dosing and administration' block added to clinical information. Version number changed to v.6

Version 5

Date	Summary of changes
05/12/2019	Reviewed at the Haematology Reference Committee meeting with the following changes: • Evidence updated to include published evidence in the HIV population. • Limited evidence table included as all trials supporting this protocol are phase II. • Day 6 Mesna removed. • References list updated. • Version changed to v.5. • Protocol to be reviewed in 2 years.

Version 4

Date	Summary of changes
25/06/2008	Changes to the wording of the administration of vincristine to reflect the Australian Council for Safety and Quality in Health Care safety alert and the NSW Health safety alert.
09/11/2008	Review and reformatting of patient information sheet.
19/03/2010	Complete review by Haematology Reference Committee and update of protocol to reflect new evidence (LY10 trial, Mead et al 2008); change to schedule of additional intrathecal treatment for proven CNS disease to follow LY10 trial; update of evidence section; transferred to eviQ.
19/10/10	Protocol updated to incorporate the consideration of the addition of rituximab in CD20+ Burkitt lymphoma.
22/03/2011	New format to allow for export of protocol information. Protocol version number changed to v.2. Antiemetics and premedications added to the treatment schedule. Additional Clinical Information, Key Prescribing table and Key Administration table combined into new section titled Clinical Considerations. Drug specific information placed behind the drug name link. Title of protocol amended to reflect acronym.
11/10/2013	Reviewed at Haematology Reference Committee meeting.
23/09/2014	Added link to ALLG, ANZCTR and Lymphoma Australia website with statement 'Patients with NHL should be considered for inclusion into clinical trials'.
28/01/2015	Additional Clinical Information "Additional intrathecal treatment for proven CNS disease with IVAC protocol" deleted. Content incorporated into the Treatment Schedule Summary section.
11/09/2015	Reviewed at Haematology Reference Committee meeting with no changes made. Review in 2 years. Drug costs updated.
31/05/2017	Transferred to new eviQ website. Version number change to v.4.

Date	Summary of changes
25/05/2018	Reviewed at Haematology Reference Committee meeting. with no significant changes, review in 2 years.
18/07/2018	Note added underneath the treatment schedule for dose modifications in patients older than 65 years.
10/10/2019	Clinical information updated with PBS expanded indications for G-CSF.

First approved: 19 October 2010
Last reviewed: 22 October 2021
Review due: 31 December 2022
Superseded: 27 January 2022

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/549
22 Nov 2023

Patient information - Burkitt lymphoma - IVAC (ifosfamide, etoposide, cytarabine)

Patient's name:

Your treatment

The treatment schedule below explains how the drugs for this treatment are given.

IVAC (ifosfamide, etoposide, cytarabine)

This treatment protocol alternates with CODOX-M protocol and usually continues for up to a total of 4 cycles of chemotherapy. Your doctor will advise you of the number of treatments you will have.

Day	Treatment	How it is given	How long it takes
1 and 2	**Cytarabine** (*sye-TARE-a-been*)	By a drip into a vein	About 3 hours TWICE a day
	Etoposide (*e-TOE-poe-side*)	By a drip into a vein	About 1 hour
	Mesna (*MES-na*)	By a drip into a vein	About 15 minutes (day 1 only)
	Ifosfamide (*eye-FOS-fa-mide*)	By a drip into a vein	About 2 hours
	Mesna	By a drip into a vein	For 24 hours
3 and 4	**Etoposide**	By a drip into a vein	About 1 hour
	Ifosfamide	By a drip into a vein	About 2 hours
	Mesna	By a drip into a vein	For 24 hours
5	**Etoposide**	By a drip into a vein	About 1 hour
	Ifosfamide	By a drip into a vein	About 2 hours
	Mesna	By a drip into a vein	For 24 hours
	Methotrexate (*meth-o-TREX-ate)*	By injection into your spine	About 2 hours
6	**Calcium folinate (Leucovorin)** *(loo-koe-VOR-in)*	Take orally for ONE dose only, 24 hours after the methotrexate injection.	About 5 minutes
7	**Granulocyte Colony Stimulating Factor** (*G-CSF*)	By injection under the skin	

When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

IMMEDIATELY go to your nearest hospital	Emergency contact details

Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	Ask your doctor or nurse from your treating team who to contact if you have a problem
• a temperature of 38ºC or higher • chills, sweats, shivers or shakes • shortness of breath • uncontrolled vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • you become unwell.	Daytime: Night/weekend: Other instructions:

During your treatment immediately tell the doctor or nurse looking after you if you get any of the following problems:

- leaking from the area where the drugs are being given
- pain, stinging, swelling or redness in the area where the drugs are being given or at any injection sites
- a skin rash, itching, feeling short of breath, wheezing, fever, shivers, or feeling dizzy or unwell in any way (allergic reaction).

Other information about your treatment

Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

Blood tests and monitoring

Anti-cancer drugs can reduce the number of blood cells in your body. You will need to have regular blood tests to check that your blood cell count has returned to normal. If your blood count is low, your treatment may be delayed until it has returned to normal. Your doctor or nurse will tell you when to have these blood tests.

Central venous access devices (CVADs)

This treatment involves having chemotherapy through a central venous access device (CVAD). Your doctor or nurse will explain this to you. For more information see the eviQ patient information sheets on CVADs.

Other medications given during this treatment

- **Anti-sickness (anti-nausea) medication:** you may be given some anti-sickness medication. Make sure you take this medication as your doctor or nurse tells you, even if you don't feel sick. This can help to prevent the sickness starting.
- **Eye drops:** you will be given eye drops to help prevent sore eyes. You will start using the eye drops before you have your first dose of cytarabine and continue to use the eye drops until 72 hours after your last dose of cytarabine.
- **Prophylaxis medication:** you may need to take some medications to prevent infection and to help prevent or reduce some of the side effects of the chemotherapy. Your doctor or nurse will tell you how and when to take these medications.
- **G-CSF:** you will be given injection(s) of a drug called G-CSF (also called filgrastim, lipegfilgrastim or pegfilgrastim) under your skin. This helps to boost your white blood cell count. Your white blood cells help to fight infection. Lipegfilgrastim and pegfilgrastim are given once. Filgrastim is given for several days until your white blood cells recover. Follow this link to read more information on how to give this injection.

Superseded treatments

This treatment is superseded meaning that better treatments have taken its place. Uncommonly superseded treatments are still used. Your doctor will explain why this treatment has been selected for you.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immediate (onset hours to days)	
Allergic reaction	• Allergic reactions are uncommon but can be life threatening. • **If you feel unwell during the infusion or shortly after it, or:** ◦ **get a fever, shivers or shakes** ◦ **feel dizzy, faint, confused or anxious** ◦ **start wheezing or have difficulty breathing** ◦ **have a rash, itch or redness of the face** **<u>While you are in hospital:</u> Tell your doctor or nurse immediately.** **<u>After you leave:</u> Contact your doctor or nurse immediately, or go to the nearest hospital Emergency Department.**
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Bone pain after G-CSF injection	• You may have discomfort or a dull ache in your pelvis, back, arms or legs. • To reduce the pain, take paracetamol before each injection. • **Tell your doctor or nurse as soon as possible if your pain is not controlled.**
Brain swelling (encephalopathy)	• You may feel: ◦ dizzy ◦ sleepy ◦ confused or agitated. • You may also get: ◦ headaches ◦ loss of balance ◦ hallucinations ◦ seizure (fits). • These symptoms are caused by the drug ifosfamide. • If you are being treated as an outpatient, try to have someone stay at home with you during the days that you are having this medicine. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**

Bladder irritation (haemorrhagic cystitis)	• You may get: ◦ blood in your urine, sometimes with blood clots ◦ pain or burning when you urinate ◦ the urge to urinate more than normal ◦ stomach or pelvic pain or discomfort. • When you go home, make sure you drink plenty of fluids (unless you are fluid restricted). • Empty your bladder often. • **Tell your doctor or nurse as soon as possible if you notice any blood in your urine.**
Nervous system changes from cytarabine	• High doses of cytarabine can affect the nervous system. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following symptoms during or soon after your treatment:** ◦ **dizziness, drowsiness or double vision** ◦ **agitation** ◦ **difficulty walking in a straight line** ◦ **difficulty writing with a pen or pencil** ◦ **jerky movements** ◦ **slow, slurred speech.**
Eye problems from cytarabine	• You may get: ◦ eye pain or irritation ◦ blurred vision ◦ watery or gritty eyes ◦ sensitivity to light. • You will be given eye drops to help prevent and control these symptoms. It is important to use these eye drops as directed. • Protect your eyes from the weather (sun and wind) by wearing sunglasses, especially if you have lost your eyelashes. • Tell your doctor or nurse if you get any of the symptoms listed above.
Taste and smell changes	• You may find that food loses its taste or tastes different. • These changes are likely to go away with time. • Do your mouth care regularly. • Chew on sugar-free gum or eat sugar-free mints. • Add flavour to your food with sauces and herbs. • Ask your doctor or nurse for eviQ patient information - Taste and smell changes during cancer treatment.

Early (onset days to weeks)

Infection risk (neutropenia)	• This treatment lowers the amount of white blood cells in your body. The type of white blood cells that help to fight infection are called neutrophils. Having low level of neutrophils is called neutropenia. If you have neutropenia, you are at greater risk of getting an infection. It also means that your body can't fight infections as well as usual. This is a serious side effect, and can be life threatening. • Wash your hands often. • Keep a thermometer at home and take your temperature regularly, and if you feel unwell. • Do your mouth care regularly. • Inspect your central line site (if you have one) daily for any redness, pus or swelling. • Limit contact with people who are sick. • Learn how to recognise the signs of infection. • Ask your doctor or nurse for eviQ patient information - Infection during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **a temperature of 38°C or higher** ◦ **chills, shivers, sweats or shakes** ◦ **a sore throat or cough** ◦ **uncontrolled diarrhoea** ◦ **shortness of breath** ◦ **a fast heartbeat** ◦ **become unwell even without a temperature.**
Low platelets (thrombocytopenia)	• This treatment lowers the amount of platelets in your blood. Platelets help your blood to clot. When they are low, you are at an increased risk of bleeding and bruising. • Try not to bruise or cut yourself. • Avoid contact sport or vigorous exercise. • Clear your nose by blowing gently. • Avoid constipation. • Brush your teeth with a soft toothbrush. • Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to. • Tell your doctor or nurse if you have any bruising or bleeding. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if you have any uncontrolled bleeding.**
Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.
Flu-like symptoms from cytarabine	• You may get a fever, skin rash, aches and pains or increased sweating. • These symptoms are caused by the drug cytarabine. • Symptoms usually happen 6 to 12 hours after your dose, and may last until 24 hours after your treatment has finished. • To reduce any pain or fever, take paracetamol, if needed. • Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to. • Tell your doctor or nurse if these symptoms do not get better after 24 hours.

Tiredness and lack of energy (fatigue)	• You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy. • Do not drive or operate machinery if you are feeling tired. • Nap for short periods (only 1 hour at a time) • Prioritise your tasks to ensure the best use of your energy. • Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted). • Try some gentle exercise daily. • Allow your friends and family to help. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Kidney damage	• This treatment can cause changes to how your kidneys work. • You will have blood tests to make sure your kidneys are working properly. • You may need to drink more fluids while you are having treatment. Your doctor or nurse will tell you if you need to do this. • **Tell your doctor or nurse as soon as possible if you notice that your urine changes colour or you don't need to empty your bladder as often.**

Mouth pain and soreness (mucositis)	• You may have:
	  ◦ bleeding gums
	  ◦ mouth ulcers
	  ◦ a white coating on your tongue
	  ◦ pain in the mouth or throat
	  ◦ difficulty eating or swallowing.
	• Avoid spicy, acidic or crunchy foods and very hot or cold food and drinks.
	• Try bland and soft foods.
	• Brush your teeth gently with a soft toothbrush after each meal and at bedtime. If you normally floss continue to do so.
	• Rinse your mouth after you eat and brush your teeth, using either:
	  ◦ 1/4 teaspoon of salt in 1 cup of warm water, or
	  ◦ 1/4 teaspoon of bicarbonate of soda in 1 cup of warm water
	• Ask your doctor or nurse for eviQ patient information - Mouth problems during cancer treatment.
	• **Tell your doctor or nurse if you get any of the symptoms listed above.**

Skin rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**

Late (onset weeks to months)	
Hair loss (alopecia)	• Your hair may start to fall out from your head and body. • Hair loss usually starts 2 to 3 weeks after your first treatment. • You may become completely bald and your scalp might feel tender. • Use a gentle shampoo and a soft brush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat, scarf or wig. • Protect your scalp from the sun with a hat or sunscreen of SPF 50 or higher. • Moisturise your scalp to prevent itching. • Ask your doctor or nurse about the Look Good Feel Better program
Low red blood cells (anaemia)	• You may feel dizzy, light-headed, tired and appear more pale than usual. • Tell your doctor or nurse if you have any of these signs or symptoms. You might need a blood transfusion. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have any chest pain, trouble breathing, or feel like your heart is racing.**
Chemo brain (chemotherapy-related cognitive impairment)	• You may notice that you are unable to concentrate, feel unusually disorganised or tired (lethargic) and have trouble with your memory. • These symptoms usually improve once treatment is completed. • Ask your doctor or nurse for eviQ patient information – Memory changes and chemotherapy (chemo brain). • Tell your doctor or nurse if you get any of the symptoms listed above.

Delayed (onset months to years)	

Lung problems	• Lung problems are rare, but can be serious. They may occur throughout treatment or after the completion of treatment.
	• You may get:
	  ◦ shortness of breath
	  ◦ fever
	  ◦ dry cough
	  ◦ wheezing
	  ◦ fast heartbeat
	  ◦ chest pain.
	• Your doctor will monitor how well your lungs are working during your treatment.
	• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**

General advice for people having cancer treatment

Chemotherapy safety

- Learn how to keep you and your family safe while you are having anticancer drugs.
- See our patient information sheet - Chemotherapy safety at home.

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking

aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet and food safety

- While you are receiving this treatment, it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.
- There are some foods that may cause infection in high risk individuals and should be avoided. For further information on foods to avoid and food hygiene please ask for a copy of the Listeria and food brochure.

Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Risk of developing a second cancer

- Some anticancer treatments can increase your chance of developing a second cancer, this is rare. Your doctor will discuss with you the specific risks of your treatment.

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support
- Call the Leukaemia Foundation on 1800 620 420 (Mon to Fri 9am – 5pm)
- Call the Lymphoma Nurse Support Line on 1800 953 081 (Mon to Fri 9am - 5pm)
- Call the Myeloma Australia Support Line on 1800 693 566 (Mon to Fri 9am - 5pm)

Haematology, transplant and cellular therapy information

- Arrow bone marrow transplant foundation – arrow.org.au
- Australasian Menopause Society – menopause.org.au
- Chris O'Brien Lifehouse - Total Body Irradiation - mylifehouse.org.au/departments/radiation-oncology/total-body-irradiation/
- Healthy Male Andrology Australia – healthymale.org.au/
- International Myeloma Foundation – myeloma.org
- Leukaemia Foundation – leukaemia.org.au
- Lymphoma Australia – lymphoma.org.au
- Myeloma Australia – myeloma.org.au
- NSW Agency for Clinical Innovation, Blood & Marrow Transplant Network – https://aci.health.nsw.gov.au/networks/bmtct
- NSW Agency for Clinical Innovation - aci.health.nsw.gov.au/projects/immune-effector-cell-service
- NCCN Guidelines for Patients Immunotherapy Side Effects: CAR T-Cell Therapy - nccn.org/patientresources/patient-resources/guidelines-for-patients
- Talk Blood Cancer – cmlsupport.org.uk/organisation-type/social-media-groups

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyondblue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- Carer Help - carerhelp.com.au
- eviQ Cancer Treatments Online – eviQ.org.au
- Food Standards Australia New Zealand: Listeria & Food Safety – foodstandards.gov.au/publications/pages/listeriabrochuretext.aspx
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
- Patient Information - patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer - targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit – iCanQuit.com.au
- Patient Information - patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

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