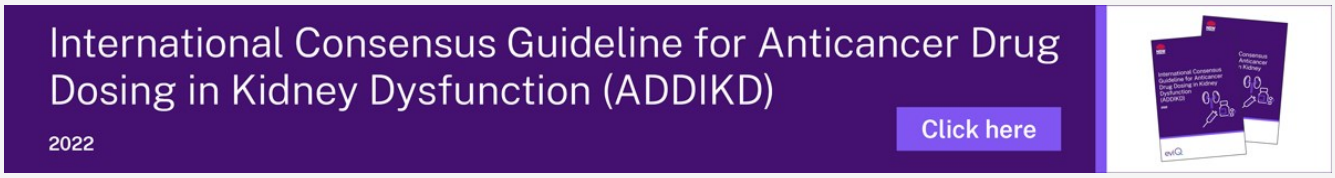
NK T-Cell lymphoma modified SMILE (dexamethasone methotrexate iFOSFamide pegaspargase etoposide)

ID: 4041 v.2 **Endorsed**

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:

- NK T-Cell lymphoma SMILE (dexamethasone methotrexate iFOSFamide asparaginase etoposide)
- Management of asparaginase therapy

Treatment schedule - Overview

Cycle 1 and 2

Drug	Dose	Route	Day
Methotrexate	2,000 mg/m^2	IV infusion	1
Calcium folinate (Leucovorin) *	15 mg/m^2 every 6 hours	IV infusion	2
Dexamethasone	40 mg ONCE a day	PO	2 to 4
Etoposide **	100 mg/m^2	IV infusion	2 to 4
iFOSFamide	1,500 mg/m^2	IV infusion	2 to 4
Mesna	300 mg/m^2	IV infusion	2 to 4
Mesna	300 mg/m^2 at 4 and 8 hours post ifosfamide dose	IV infusion	2 to 4
Filgrastim	5 micrograms/kg	Subcut	6 and continue daily until neutrophil recovery
Pegaspargase	1,500 Units/m^2 ***	IM ****	8

* Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L

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

*** This dose has been selected by the expert reference panel based on local practice. However, the dose of pegaspargase used in studies ranges between 1500 and 2500 Units/m^2.

**** Intramuscular (IM) injection is the preferred route of administration due to the lower incidence of hepatotoxicity, coagulopathy, and gastrointestinal and renal disorders, compared to the intravenous route.[1, 2] Pegaspargase can be administered intravenously over 1 - 2 hours.

Frequency: 21 days

Cycles: 2 to 6 cycles

Notes:

- Sequential radiation therapy should follow mSMILE in patients with localised disease and be considered in those with advanced-stage disease with bulky disease. Consider consolidative autologous stem cell transplant in patients with advanced stage disease achieving first remission (CR1).[3, 4, 5, 6]
- Patients that develop hypersensitivity to pegaspargase may be able to switch to erwinia asparaginase and revert to the administration schedule of ID 1552 SMILE (dexamethasone methotrexate iFOSFamide asparaginase etoposide).
- The frequency in this protocol has been selected based on studies by Ghione et al.[4] and Qi et al.[3], however the frequency may be extended to 28 days at the discretion of the clinician.

Drug status: **Methotrexate, ifosfamide, calcium folinate, dexamethasone, mesna** and **etoposide** are on the PBS general schedule

Pegaspargase: Not TGA approved or PBS reimbursed for this indication

Filgrastim: (PBS authority)

Dexamethasone is available as **0.5 mg** and **4 mg** tablets

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.*

Cycle 1 and 2

Day 1		
Methotrexate	2,000 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 6 hours
Day 2		
Calcium folinate (Leucovorin)	15 mg/m^2 (IV infusion)	Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L
Dexamethasone	40 mg (PO)	ONCE a day on days 2 to 4. Take in the morning with food.
Etoposide	100 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 1000 mL sodium chloride 0.9% over 6 hours (loaded with mesna)
Mesna	300 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 6 hours (loaded with ifosfamide)
Mesna	300 mg/m^2 (IV infusion)	in 100 mL sodium chloride 0.9% at 4 and 8 hours after completion of EACH ifosfamide dose
Day 3 and 4		
Dexamethasone	40 mg (PO)	ONCE a day on days 2 to 4. Take in the morning with food.

Day 3 and 4		
Etoposide	100 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 1000 mL sodium chloride 0.9% over 6 hours (loaded with mesna)
Mesna	300 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 6 hours (loaded with ifosfamide)
Mesna	300 mg/m^2 (IV infusion)	in 100 mL sodium chloride 0.9% at 4 and 8 hours after completion of EACH ifosfamide dose
Day 6		
Filgrastim	5 micrograms/kg (Subcut)	inject subcutaneously on day 6 and continue daily until neutrophil recovery.
Day 8		
Pegaspargase	1,500 Units/m^2 (IM)	inject intramuscularly. Rotate site of administration.*

*Intramuscular (IM) injection is the preferred route of administration due to the lower incidence of hepatotoxicity, coagulopathy, and gastrointestinal and renal disorders, compared to the intravenous route.[1, 2] Pegaspargase can be administered intravenously over 1 - 2 hours.

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

Frequency: 21 days

Cycles: 2 to 6 cycles

Indications and patient population

Indications:

- Newly diagnosed stage IV or relapsed/refractory extranodal natural killer/T-cell lymphoma
- Newly diagnosed localised extranodal natural killer/T-cell lymphoma in combination with radiation therapy

Contraindications:

Pegaspargase should not be used in patients who have:

- previous anaphylaxis or severe hypersensitivity to asparaginase formulations
- severe hepatic impairment
- existing or a history of pancreatitis
- previous haemorrhagic or severe thrombotic events.

Cautions/exclusions:

- Pegaspargase should be used with caution in patients over 40 years of age and in those with a body mass index (BMI) greater than 30 due to an increased risk of side effects.
- The modified SMILE (mSMILE) regimen is associated with significant haematological and non-haematologic toxicity and careful consideration of patient fitness for this regimen is recommended.

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. High risk with pegaspargase. Hypersensitivity reactions may occur, e.g. life-threatening anaphylaxis, particularly in patients with known hypersensitivity to the other forms of asparaginase. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction. Patients that develop hypersensitivity to the E. coli derived formulation may be able to switch to Erwinia asparaginase. Read more about Management of asparaginase therapy 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
Pre-hydration	Pre-hydration with sodium bicarbonate 8.4% infusion. Urinary pH must be greater than 7 prior to commencing methotrexate infusion. Consider prescribing sodium bicarbonate oral capsules for administration prior to methotrexate infusion. Sodium bicarbonate 8.4% should continue until the methotrexate level is equal to or less than 0.1 micromol/L. Read more about high dose methotrexate-induced toxicity.
Methotrexate interactions	Avoid administering the following drugs in combination with high dose methotrexate: ciprofloxacin, NSAIDs, probenecid, proton pump inhibitors (PPIs) (e.g. esomeprazole, omeprazole, pantoprazole), sulphonamides (e.g. sulfamethoxazole (in Bactrim®, Septrin®)), penicillins (e.g. piperacillin (in Tazocin®)) and trimethoprim. Severe mucositis may occur if administered together.
High dose methotrexate	Monitoring of methotrexate levels is essential as delayed methotrexate excretion is potentially an emergency situation. Methotrexate levels to be monitored every 24 hours until level is less than 0.1 micromol/L. Methotrexate is renally eliminated. Kidney function must be evaluated prior to treatment. Methotrexate exits slowly from third space compartments (e.g. pleural effusions or ascites), resulting in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels. Glucarpidase is recommended in patients with high dose methotrexate (HDMTX)-induced acute kidney injury and delayed methotrexate clearance. It can rapidly lower methotrexate levels and early administration within 48 to 60 hours from the start of the HDMTX infusion is critical, as life-threatening toxicities may not be preventable beyond this time point.[7] Read more about high dose methotrexate-induced toxicity.
Pegaspargase	Pegaspargase is associated with numerous toxicities including hypersensitivity, hepatotoxicity, coagulation abnormalities, pancreatitis, hyperlipidaemia, hyperglycaemia and CNS effects. Therefore routine monitoring and assessment of several parameters are required throughout treatment. For comprehensive information on formulations, dosing, interactions, adverse reactions and specific monitoring parameters for asparaginase, see Management of asparaginase therapy document.

Pancreatitis	Pancreatitis (both haemorrhagic or necrotising) has been reported in patients receiving pegaspargase with fatal outcomes. If pancreatitis is suspected pegaspargase should be discontinued and not restarted if confirmed. Serum amylase and/or lipase measurements should be performed frequently to identify early signs of pancreatic inflammation. If treatment is discontinued due to pancreatitis, appropriate investigations (e.g. ultrasound) should be performed at least four months following termination of therapy.
Thrombotic events	Increased prothrombin time (PT), increased activated partial thromboplastin time (APTT), and hypofibrinogenaemia may occur in patients receiving pegaspargase. A baseline coagulation profile (including antithrombin III) should be established and then periodically monitored during and after treatment according to local policy. Patients should be on thromboprophylaxis with enoxaparin to prevent thrombotic events unless contraindicated. Serious thrombotic events may occur in patients receiving pegaspargase; in the event of CNS thrombosis, discontinuation of pegaspargase should be strongly considered. Read more about Management of asparaginase therapy
Hepatotoxicity	Caution is required when pegaspargase is given in combination with other hepatotoxic substances. If pegaspargase is given in combination with hepatotoxic substances, the patient should be closely monitored for liver impairment, especially if there is pre-existing hepatic impairment.
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
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
Etoposide conversion factor	Doses in this protocol are expressed as etoposide. Note: Etopophos (etoposide phosphate) 113.6 mg is equivalent to etoposide 100 mg. Etoposide phosphate is the preferred formulation for this protocol, as solutions of conventional etoposide would exceed the maximum concentration of 0.4 mg/mL and may precipitate. All administration details in this protocol refer to etopophos.
Corticosteroids	Diabetic patients should monitor their blood glucose levels closely. To minimise gastric irritation, advise patient to take immediately after food. Consider the use of a H2 antagonist or proton pump inhibitor if appropriate. Read more about acute short term effects from corticosteroids
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	Assess patient for risk of developing tumour lysis syndrome. Read more about the prevention and management of tumour lysis syndrome.
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	Read more about antiviral prophylaxis drugs and doses

Antifungal prophylaxis	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 product support	The use of FFP and cryoprecipitate may be required to maintain fibrinogen levels to a normal range. Read more about Management of asparaginase therapy
Blood tests	FBC, EUC, eGFR, BSL, LDH, uric acid, albumin, triglycerides and total cholesterol levels at baseline and prior to each cycle. LFTs, bilirubin, lipase, amylase, APTT, PT, INR, fibrinogen, antithrombin III levels at baseline and at least once or twice a week as clinically indicated. Monitor methotrexate levels every 24 hours until the level is less than 0.1 micromol/L.
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	
Platelets x 10^9/L (nadir)	
less than 25	Consider reducing the dose of methotrexate, ifosfamide and etoposide by 33% in the second cycle. Cease pegaspargase and administer in second cycle if platelets recover

Renal impairment	
Creatinine clearance (mL/min)	
15 to less than 50	Reduce etoposide by 25%
less than 30	Reduce ifosfamide by 25%
Creatinine clearance must be greater than 80 mL/min prior to administration of full dose high dose methotrexate. It is advised to reduce the methotrexate dose in proportion to the calculated creatinine clearance when this is less than 80 mL/min e.g. if creatinine clearance is 75 mL/min, then 75% of the calculated methotrexate dose is given.[8] Methotrexate is contraindicated if CrCL is less than 30 mL/min	

Hepatic impairment	
Hepatic dysfunction	
Mild or moderate	Use etoposide with caution
Severe	Consider continuing etoposide without dose reduction for patients with NK T-Cell lymphoma associated haemaophagocytic syndrome[9] Pegaspargase contraindicated if bilirubin > 3 x ULN or transaminases > 10 x ULN

Mucositis, stomatitis and diarrhoea	
Grade 3 or Grade 4	Diarrhoea and ulcerative stomatitis require interruption of therapy otherwise haemorrhagic enteritis and death from intestinal perforation may occur: reduce methotrexate by 25%

Methotrexate	
Concentration greater than 1 x 10^{-7} mmol/L (72 hours after administration in the first course)	Reduce methotrexate dose by 33%

Pegaspargase-related reactions	
Grade 1 local allergic reactions not requiring intervention	Continue pegaspargase
Grade 2 or greater systemic reactions	Consider discontinuation of pegaspargase and substitute with erwinia asparaginase if available
Grade 3 or 4 allergic reaction/hypersensitivity (such as anaphylaxis), pancreatitis or thrombotic events	Discontinue pegaspargase, if discontinued due to allergy/hypersensitivity only, consider changing to erwinia asparaginase.
Pegaspargase should not be withheld for asymptomatic coagulation laboratory abnormalities. Cryoprecipitate and anti-thrombin III infusions may be required. Refer to Management of asparaginase therapy.	

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*

Dexamethasone		
	Interaction	**Clinical management**
CYP3A4 interactions	Dexamethasone is a substrate of CYP3A4 and a weak to moderate inducer of CYP3A4. The clinical relevance of CYP3A4 induction by dexamethasone is unknown as the mechanism has yet to be established	The effects of the concomitant use of dexamethasone with other CYP3A4 inducers, inhibitors or substrates is variable. If used concomitantly, monitor patients closely for adverse drug reactions
Warfarin	Concurrent use may result in increased risk of bleeding or diminished effects of warfarin	Monitor prothrombin time / INR (especially during initiation or discontinuation) and for signs of drug toxicity during concomitant use; adjust warfarin dose as required
Oral hypoglycaemics	Corticosteroids may cause hyperglycaemia and worsen diabetes control	Monitor blood glucose levels and adjust oral hypoglycaemic dose as required

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,	Increased toxicity of ifosfamide possible due to increased conversion to active	Avoid combination or monitor for ifosfamide toxicity

Ifosfamide		
St John's wort etc.)	and toxic metabolites	
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

Methotrexate		
	Interaction	**Clinical management**
Ciprofloxacin **NSAIDS** **Probenecid** **Proton pump inhibitors (e.g. esomeprazole, omeprazole, pantoprazole)**	Increased toxicity of methotrexate possible due to reduced clearance	Avoid combination or monitor for methotrexate toxicity Important note: with high-dose methotrexate therapy, many of these drug combinations are *contraindicated*
Sulphonamides and penicillins (e.g. sulfamethoxazole (in Bactrim®, Septrin®), piperacillin (in Tazocin®) etc.)	Increased toxicity of methotrexate possible due to displacement from serum protein binding	Avoid combination or monitor for methotrexate toxicity
Trimethoprim	Increased toxicity of methotrexate possible due to additive antifolate activity	Avoid combination or monitor for methotrexate toxicity
Mercaptopurine	Increased toxicity of mercaptopurine possible due to reduced clearance	Avoid combination or monitor for mercaptopurine toxicity
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
Hepatotoxic drugs (e.g. azathioprine, leflunomide, retinoids, sulfasalazine)	Additive hepatotoxicity	Avoid combination or monitor liver function closely
Folic acid (e.g. as in multivitamins) **Asparaginase (administered immediately prior or concurrently)**	Reduced efficacy of methotrexate possible due antagonism of its action	Avoid combination or monitor for decreased clinical response to methotrexate Note: asparaginase administered shortly after methotrexate can enhance its efficacy and reduce its toxicity
Infliximab	Altered methotrexate concentration	Monitor for signs of methotrexate toxicity or reduced efficacy

Pegaspargase		
There are no documented interactions for pegaspargase. However, a range of clinical effects can occur due to the mechanism of action of pegaspargase.		
Clinical effect	**Action**	**Clinical management**
Effect on use with other chemotherapy agents	Pegaspargase may affect the action of other cytotoxic drugs requiring cell division for their effect (i.e. methotrexate, cytarabine). This effect can be either synergistic or antagonistic, depending on the timing of administration of the agents.	Adherence to the treatment schedule is recommended to minimise these potential interactions.
	Immediately preceding or concomitant treatment with vincristine can increase the toxicity of pegaspargase and increases the risk of anaphylactic reactions.	Administer vincristine 12 hours prior to pegaspargase to minimise toxicity.
Effects on protein-bound drugs	Due to its effects on protein synthesis and hepatic function, pegaspargase can potentially interfere with metabolism and clearance of other drugs including chemotherapy drugs known to interact with CYP enzymes.	Monitor for hepatotoxicity if used concomitantly.
Coagulation effects	Use of pegaspargase can lead to fluctuating levels of coagulation factors. This may increase the risk of bleeding and/or thrombosis.	Caution is needed when anticoagulants are given concomitantly.
	Alterations in coagulation parameters can be more pronounced when glucocorticoids (e.g. prednisolone) and pegaspargase are given concomitantly.	Monitor levels of coagulation parameters such as fibrinogen and ATIII
Oral contraceptive effects	Pegaspargase hepatotoxicity may impair the hepatic clearance of oral contraceptives.	Concomitant use of pegaspargase and oral contraceptives is not recommended. A method other than oral contraception should be used in women of childbearing potential
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

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.

Day 1

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require delay of treatment and review by medical officer before commencing 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
- strict fluid balance
- dipstick urinalysis to monitor pH:
  - prior to treatment
  - on all urine output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Methotrexate

Prehydration:

- administer 100 mL sodium bicarbonate 8.4% in 1000 mL glucose 5% OR sodium chloride 0.9% over 4 hours
- continue hydration with sodium bicarbonate 8.4% as prescribed
- when urine pH is greater than 7 commence methotrexate

If the urine pH drops below 7 during the methotrexate infusion:

- administer stat dose of 100 mL sodium bicarbonate 8.4% over 15 minutes
- continue to test all urine for pH, if the pH continues to drop below 7 seek medical review as further doses of sodium bicarbonate may be required.
- the starting time of the methotrexate infusion must be documented as the calcium folinate (leucovorin) rescue is to commence exactly 36 hours after the start of the methotrexate and continue until the methotrexate level is less than 0.1 micromol/L

Methotrexate

- Administer via IV infusion over 6 hours
- flush with ~50 mL of sodium chloride 0.9%

Post methotrexate:

- continue hydration with sodium bicarbonate 8.4% until methotrexate level is less than 0.1 micromol/L
- continue to monitor all urine pH and fluid input and output
- monitor methotrexate concentration every 24 hours until the level is less than 0.1 micromol/L

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

Days 2 to 4

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require delay of treatment and review by medical officer before commencing 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:
  - prior to treatment for haematuria and pH level
  - on all urine output to monitor pH

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Treatment - Time out

Calcium Folinate (Leucovorin)

- administer by IV bolus via a side port of the IV line over 1 to 2 minutes
- flush with ~ 50mL of sodium chloride 0.9%.

Note: Start calcium folinate (leucovorin) rescue 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

Dexamethasone

- administer orally ONCE a day in the morning
- to be taken with or immediately after food.

Note: if a dose is forgotten or vomited, contact treating team.

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) with mesna:

- via IV infusion over 6 hours
- flush with ~100 mL of sodium chloride 0.9%

IV mesna

- administer mesna via IV bolus at 4 and 8 hours post completion ifosfamide/mesna infusion
- flush with ~100 mL of sodium chloride 0.9%

Deaccess CVAD.

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

Day 6

Filgrastim

- inject subcutaneously ONCE daily, and until neutrophil recovery

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Day 8

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require delay of treatment and review by medical officer before commencing treatment.

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Pegaspargase

- administer via intramuscular (IM) injection (alternatively may be administered intravenously over 1 to 2 hours)
- when administered IM, the volume at the injection site should be less than or equal to 2 mL; if volume to administer is larger than 2 mL, use multiple injection sites and ensure site rotation

Note: monitor patient during and for one hour after drug administration, as anaphylaxis may occur. Ensure immediate access to emergency / adverse-reaction kit is available.

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

Discharge information

Antiemetics

- Antiemetics as prescribed.

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)	
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
Headache	
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
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Injection-site reactions	Inflammation of or damage to the tissue surrounding the area where a drug was injected.
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Taste and smell alteration	Read more about taste and smell changes

Early (onset days to weeks)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
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
Abdominal pain	Dull ache, cramping or sharp pains are common with some anti-cancer drugs. These are caused by either increased or decreased gastrointestinal motility and can be associated with diarrhoea or constipation.
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Diarrhoea	Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
Fluid retention and oedema	An excess amount of fluid around the cells, tissues or serous cavities of the body, leading to swelling.
Hepatotoxicity	Anti-cancer drugs administered either alone or in combination with other drugs and/or radiation may cause direct or indirect hepatotoxicity. Hepatic dysfunction can alter the metabolism of some drugs resulting in systemic toxicity.
Hyperbilirubinaemia	An abnormal increase in the amount of bilirubin circulating in the blood which may result in jaundice.
Hyperglycaemia	High blood sugar, an excess of glucose in the blood stream.

Hyperlipidaemia and hypercholesterolaemia	Abnormally elevated levels of lipids and cholesterol in the blood.
Hypoalbuminaemia	Abnormally low levels of albumin in the blood.
Hypokalaemia	Abnormally low levels of potassium in the blood.
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
Pancreatitis	Inflammation of the pancreas with impairment of function is associated with asparaginase formulations.
Peripheral neuropathy	Typically symmetrical sensory neuropathy, affecting the fingers and toes, sometimes progressing to the hands and feet. It is associated with several classes of anti-cancer drugs. These include taxanes, platinum-based compounds, vinca alkaloids and some drugs used to treat multiple myeloma. Read more about peripheral neuropathy
Photosensitivity	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
Side effects of corticosteroids	Insomnia, oedema, increased risk of infection e.g. oral thrush, gastric irritation, worsening of peptic ulcer disease, increased blood sugar levels, loss of diabetic control, mood and behavioural changes - including anxiety, euphoria, depression, mood swings, increased appetite and weight gain, osteoporosis and fractures (long term use), bruising and skin fragility are associated with corticosteroid use.
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
Thromboembolism	Serious thromboembolic events can occur in patients receiving pegaspargase. The majority of thromboses occur in the CNS. Patients should be carefully assessed for risk factors with baseline and regular monitoring of coagulation profile (including PT, APTT, fibrinogen, antithrombin III) during and after treatment. Antithrombotic prophylaxis is recommended. Read more about Management of asparaginase therapy

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
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)
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

A search of the literature found limited evidence for the use of SMILE and modified SMILE (mSMILE) for the treatment of extranodal natural killer/T-cell lymphoma (ENKTL). The strongest level of evidence available has been the Phase II study by Kwong et al.,[10] upon which the expert reference panel supported the existing eviQ SMILE protocol.

Treatment of ENTKL has been historically suboptimal owing to the high level of multi-drug resistance of natural killer (NK) cells conferred by their high expression of p-glycoprotein. The incorporation of L-asparaginase, a non-P glycoprotein dependent drug,

has been effective in overcoming the multi-drug resistant nature of ENTKL. The SMILE protocol has become the standard of care for treatment of advanced-stage ENKTL and has been used in two phase II studies with a reported overall response rate (ORR) of 79-81% and complete response (CR) of 50-56% after 2-3 cycles.[10, 11] The Asia lymphoma study group has reported the largest cohort of ENTKL patients studied to date, with a total of 87 patients, 43 newly diagnosed and 44 relapsed/refractory. A median of 3 courses of SMILE were administered. After 2-3 cycles, the ORR was 78%, with a CR of 56%. On treatment completion, the ORR became 81% (CR 66% and PR 15%). At a median follow up of 31 months, the 5-year overall survival (OS) was 50%, and the 4-year disease-free survival (DFS) was 64%. Of note, the SMILE regimen is associated with significant toxicity with reported grade 3-4 neutropenia in 72.7% and treatment-related mortality (TRM) of 7%.[10]

Since the publication of Kwong et al. 2012, there have been modifications to the SMILE protocol (mSMILE), which have been reported only in single centre retrospective studies.[3, 4] In mSMILE the 7 doses of L-asparaginase (colaspase) have been replaced by a pegylated formation, pegaspargase. These two studies are the only published experiences with the mSMILE protocol to date and have been referenced in the National Comprehensive Cancer Network (NCCN) T-cell lymphoma guideline's endorsement of mSMILE for ENKTL.[12] The rationale for this substitution reflects not only improved ease of administration, but also lower rates of infusion reaction and longer half-life which allow for a more favourable toxicity profile than L-asparaginase.[5] Furthermore, as of 2019, L-asparaginase (colapase) is no longer available in Australia, and the alternative *erwinia* derived asparaginase has been subject to recurrent severe global shortages. This has necessitated review and development of the mSMILE protocol that incorporates pegaspargase.

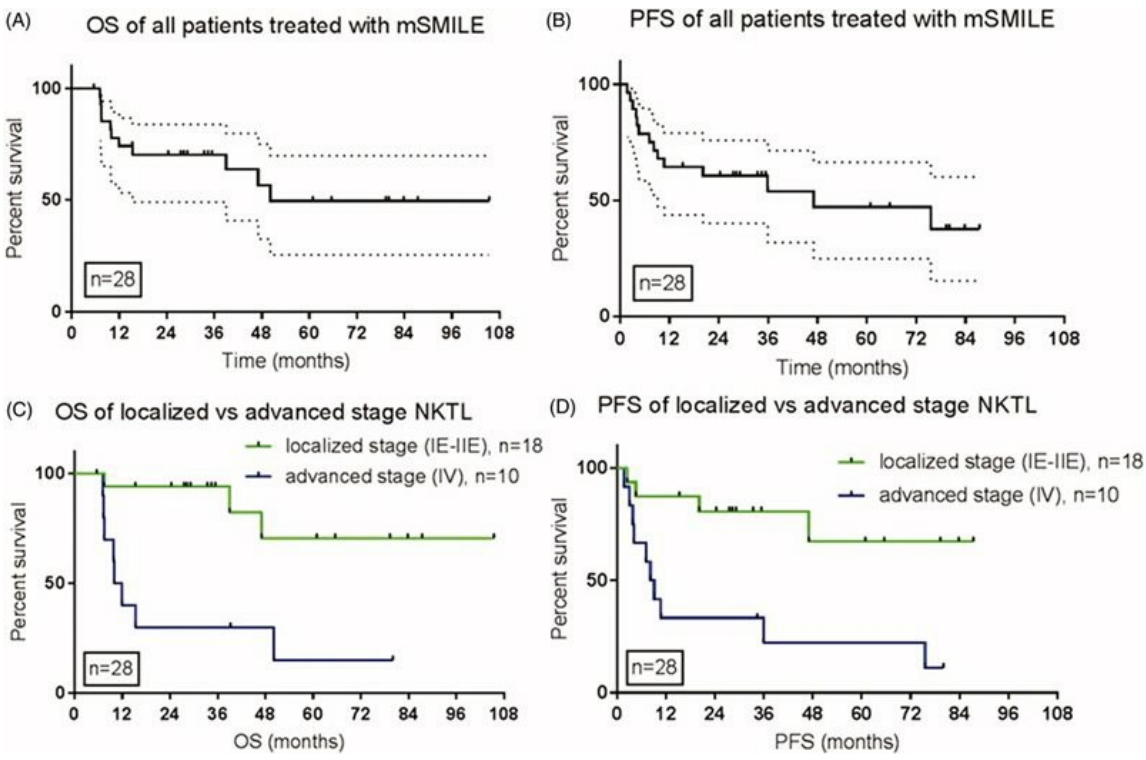
Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
Phase II trials	Yamaguchi et al. 2011[11]	**Yes**	Yes (L-asparaginase based)	L- asparaginase days 8,10,12,14,16,18,20 Leucovorin 15 mg x 4 days 2 to 4
	Kwong et al. 2012[10]	**Yes**	Yes (L-asparaginase based)	L- asparaginase days 8,10,12,14,16,18,20 Leucovorin 45 mg/day days 2 to 4 Mesna 900 mg/m^2 days 2 to 4
Retrospective studies	Qi et al. 2016[3]	**Yes**	Yes	2-6 cycles +/- intensity-modulated radiotherapy (IMRT)
	Ghione et al. 2020[4]	**Yes**	Yes	Early stage diagnosis: 2 cycles + IMRT Advance disease: 3-4 cycles +/- IMRT
Guidelines	**Date published/revised**	**Supports Use**	**Is the dose and regimen consistent with the protocol?**	**Comments**
NCCN	Oct 2020	**Yes**	N/A	Version 1.2021
BCCA	May 2021	**Yes**	Yes	28 day cycle
CCO	N/A	**N/A**	N/A	-

Efficacy

The Memorial Sloan Kettering Cancer Centre has utilised the mSMILE approach substituting L-asparaginase with pegaspargase and shortening the cycle length from 28 to 21 days since 2009. This approach also incorporated a lower dose of radiation therapy at 45Gy for patients with limited-stage disease or those with advanced-stage and bulky nasopharyngeal disease. Their experience was initially presented at ASH 2011 in abstract form,[6] thereafter published as a retrospective cohort study in 2016 and since

updated in 2020.[3, 4] The initial study demonstrated that mSMILE resulted in significantly higher CR rate than accelerated CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) 80% vs 30% (p=0.015). A subsequent study of patients treated with mSMILE from 2009 to 2019 reported ORR of 93% with a CR rate of 68%. When all patients were considered together, the 5 year OS was 49.6% with 5 year PFS of 46.8%. After median follow up of 31 months, patients with localised disease had a favourable outcome with OS of 100% and PFS 92%. Median OS and progression-free survival (PFS) in patients with advanced disease was 11 and 8 months, respectively.

Figure 1. Overall survival (OS) and progression-free survival (PFS) of population treated with mSMILE[4]



Toxicity

Grade 3-4 toxicity was reported in 75% of patients with no TRM seen.[4]

Table 1. Toxicities in patients treated with mSMILE[4]

Toxicity category	All patients (all mSMILE cycles), n (%)		
Grade	**Any**	**3**	**4**
Hematologic ($n = 28$)			
Neutropenia	28 (100)	9 (34)	8 (30)
Anemia	24 (88)	2 (7)	6 (23)
Thrombocytopenia	24 (88)	1 (4)	4 (15)
Non-hematologic ($n = 28$)			
Nausea	8 (28)	0	0
Fatigue	7 (25)	0	0
Diarrhea	5 (17)	2 (7)	0
Neutropenic fever	4 (14)	4 (14)	0
Transaminase elevation	4 (14)	1 (3)	0
Encephalopathy (ifosfamide)	4 (14)	2 (7)	0
Mucositis	3 (11)	0	0
Sinus bradycardia	3 (11)	0	0
Acute kidney injury (methotrexate)	3 (11)	2 (7)	1 (3)
Allergic reaction (PEG-asparaginase)	2 (7)	2 (7)	0
Diabetes imbalance (steroids)	1 (3)	1 (3)	0
Pneumonia	1 (3)	0	1 (3)
Deep venous thrombosis	1 (3)	0	0
Atrial fibrillation	1 (3)	0	0
Systemic infection (Sepsis)	1 (3)	0	1 (3)
Meningitis	1 (3)	0	1 (3)
SIADH	1 (3)	1 (3)	0
Neuropathy	1 (3)	0	0

SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion.

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History

Version 2

Date	Summary of changes
04/05/2023	Methotrexate target level updated. Version number changed to v.2
31/05/2023	Reviewed electronically by Haematology Reference Committee. Nil changes. Review in 4 years.

Version 1

Date	Summary of changes
22/10/2021	New protocol presented at Haematology Reference Committee meeting.

Date	Summary of changes
31/03/2022	Protocol approved and published on eviQ as version 1. For review in 1 year.
23/11/2022	Pegaspargase drug interaction updated.

First approved: 31 March 2022
Last reviewed: 28 April 2023
Review due: 30 June 2027

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/4041
26 Nov 2023

Patient information - Natural killer/T-Cell lymphoma - Modified SMILE (dexamethasone, methotrexate, ifosfamide, pegaspargase, etoposide)

Patient's name:

Your treatment

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

Modified SMILE (dexamethasone, methotrexate, ifosfamide, pegaspargase, etoposide)			
This treatment cycle is repeated every 21 days. Your doctor will advise you of the number of treatments you will have.			
Day	**Treatment**	**How it is given**	**How long it takes**
1	**Methotrexate** (*Meth-o-TREX-ate*)	By a drip into a vein	About 6 hours
2	**Calcium folinate (Leucovorin)** (loo-koe-VOR-in)	By a drip into a vein	About 5 minutes every SIX hours
2, 3 and 4	**Dexamethasone** (*dex a METH a sone*)	Take orally ONCE a day in the morning on days 2 to 4. To be taken with or immediately after food. If you forget to take your tablets or vomit your tablets, contact your treating team.	
	Etoposide (*e-TOE-poe-side*)	By a drip into a vein	About 30 minutes to 1 hour
	Ifosfamide (*eye-FOS-fa-mide*)	By a drip into a vein	About 6 hours
	Mesna (*MES-na*)	By a drip into a vein	
	Mesna (*MES-na*)	By a drip into a vein	At 4 hours and 8 hours after completion of ifosfamide infusion
6	**Granulocyte Colony Stimulating Factor** (*G-CSF*)	By injection under the skin	About 5 minutes
8	**Pegaspargase** (*peg-AS-par-jase*)	By injection into a large muscle	About 5 to 10 minutes

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 Department, or contact your doctor or nurse if you have any of the following at any time:	**Emergency contact details** Ask your doctor or nurse from your treating team who to contact if you have a problem
• a temperature of 38°C or higher • chills, sweats, shivers or shakes • shortness of breath	Daytime:..... Night/weekend:..... Other instructions:.....

- uncontrolled vomiting or diarrhoea
- pain, tingling or discomfort in your chest or arms
- you become unwell.

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.
- **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.

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)

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.**
Headache	• You can take paracetamol if you have a headache. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get a very bad headache that is not helped by pain medication.**
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.**
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.**
Injection-site reaction	• At the injection site you may get pain, redness, swelling or bruising. • These symptoms are usually not serious. • **Tell your doctor or nurse immediately if you notice any redness or pain during or after treatment.**
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.**

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)	
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.**
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.**
Stomach pain	• You may get: ◦ dull aches ◦ cramping or pain ◦ bloating or flatulence (gas). • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have stomach pain that you are unable to control.**

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.
Diarrhoea	• You may get bowel motions (stools, poo) that are more frequent or more liquid. • You may also get bloating, cramping or pain. • Take your antidiarrhoeal medication as directed by your doctor. • Drink plenty of fluids (unless you are fluid restricted). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • Ask your doctor or nurse for eviQ patient information - Diarrhoea during cancer treatment. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.**
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.**
Extra fluid in the body (fluid retention)	• You may gain weight over a short amount of time. • Your hands and feet may become swollen, appear red or feel hot and uncomfortable. • Wear loose clothing and shoes that are not too tight. • Try not to stand up or walk around too much at one time. • If your ankles or legs get swollen, try raising them. • Make sure that any cuts or areas of broken skin are treated as soon as possible. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above or gain 1 to 2 kg in a week.** • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if you become short of breath.**
Liver problems	• You may get: ◦ yellowing of your skin or eyes ◦ itchy skin ◦ pain or tenderness in your stomach ◦ nausea and vomiting ◦ loss of appetite • You will have regular blood tests to check how well your liver is working. • **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes look yellow, or if you have stomach pain.**
High blood bilirubin levels (hyperbilirubinaemia)	• You may get: ◦ yellowing of your skin or eyes ◦ itchy skin ◦ pain or tenderness in your stomach ◦ nausea and vomiting ◦ loss of appetite. • You will have regular blood tests to check how well your liver is working. • **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes look yellow, or if you have stomach pain.**

High blood sugar level (hyperglycaemia)	• You may feel thirsty and need to urinate more often than normal. • You may get repeated infections, especially thrush. • If you are a diabetic you will need to have your blood sugar levels checked more often. You may also need to have your diabetes medication increased. • **Tell your doctor or nurse if you get any of the signs or symptoms listed above.**
High blood cholesterol levels	• This treatment may increase your blood cholesterol levels. This is not a side effect you will notice. • Your cholesterol levels will be checked during your treatment.
Low blood potassium levels (hypokalaemia)	• This may be found from your routine blood tests and treated by your doctor. • If it is severe you may get: ◦ muscle cramps or twitches ◦ constipation ◦ confusion ◦ an irregular heartbeat. • **Tell your doctor or nurse as soon as possible if you get any of the signs or 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.**
Inflamed pancreas (pancreatitis)	• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get:** ◦ **abdominal (stomach) pain** ◦ **a swollen stomach** ◦ **nausea or vomiting** ◦ **fever or chills** ◦ **a fast heartbeat.**

Nerve damage (peripheral neuropathy)	• You may notice a change in the sensations in your hands and feet, including:
	  ◦ tingling or pins and needles
	  ◦ numbness or loss of feeling
	  ◦ pain.
	• You may find it difficult to do everyday activities, such as doing up buttons or picking up small objects.
	• Test water temperature with your elbow when bathing to avoid burns.
	• Use rubber gloves, pot holders and oven mitts in the kitchen.
	• Wear rubber shoes or boots when working in the garden or garage.
	• Keep rooms well lit and uncluttered.
	• Ask your doctor or nurse for eviQ patient information – Nerve problems during cancer treatment.
	• Tell your doctor or nurse if you get any of the symptoms listed above.

Skin that is more sensitive to the sun (photosensitivity)	• After being out in the sun you may develop a rash like a bad sunburn. • Your skin may become red, swollen and blistered. • Avoid direct sunlight. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher. • **Tell your doctor or nurse if you get any of the symptoms listed above.**

Side effects from steroid medication	• Steroid medication may cause:
	  ◦ mood swings and behaviour changes
	  ◦ an increased appetite
	  ◦ weight gain
	  ◦ swelling in your hands and feet
	  ◦ stomach upsets
	  ◦ trouble sleeping
	  ◦ fragile skin and bruising
	  ◦ an increase in your blood sugar level
	  ◦ weak and brittle bones (osteoporosis)
	• Take your steroid medication with food to reduce stomach upset
	• If you have diabetes, your blood sugar levels may be tested more often.
	• 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.**

Blood clots (thromboembolism)	• Blood clots can occur with this 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:**
	  ◦ **redness, heat or pain in your leg(s)**
	  ◦ **numbness or weakness in your face, arm or leg**
	  ◦ **chest pain**
	  ◦ **sudden shortness of breath**
	  ◦ **dizziness**
	  ◦ **trouble speaking**
	  ◦ **blurred vision**
	  ◦ **severe headache**
	  ◦ **unexplained falls or loss of balance.**

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
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.
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

Additional notes:

First approved: 31 March 2022
Last reviewed: 28 April 2023
Review due: 30 June 2027

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/pi/4041
26 Nov 2023