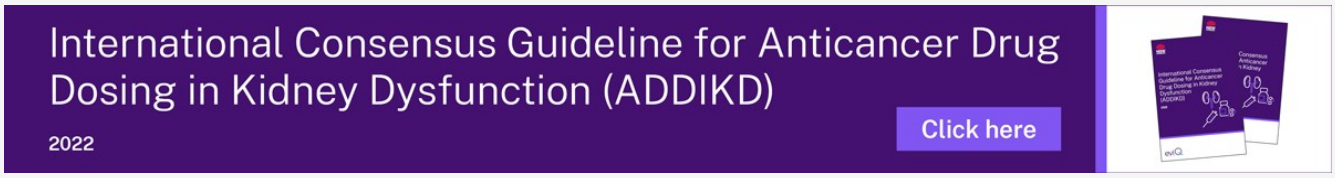
Primary CNS lymphoma (PCNSL) MATRix (methotrexate cytarabine thiotepa and rituximab)

ID: 3374 v.5 **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:

- Autologous conditioning CNS lymphoma carmustine and thiotepa
- Primary CNS lymphoma (PCNSL) whole brain consolidation EBRT

Treatment schedule - Overview

Cycle 1 to 4

Drug	Dose	Route	Day
Rituximab	375 mg/m^2	IV infusion	-5 and 0
Methotrexate	500 mg/m^2	IV infusion	1
Methotrexate	3,000 mg/m^2	IV infusion	1
Calcium folinate (Leucovorin)	15 mg/m^2 every 6 hours *	IV bolus	2
Cytarabine (Ara-C)	2,000 mg/m^2 TWICE a day	IV infusion	2 and 3
Thiotepa	30 mg/m^2	IV infusion	4

* Commence 24 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L

Frequency: 21 days

Cycles: 4

Notes:

- This is an intensive protocol. It is designed to be given as induction therapy followed by consolidation therapy with either high dose therapy and autologous stem cell transplant or whole brain radiation therapy (WBRT).
- A series of 88 'real world' patients (median age 61 years, range 28 to 76 years) from 9 European countries reported at ASH 2017 showed MATRix was feasible and effective for newly diagnosed PCNSL in routine practice however dose modifications were required in 40-54% of patients and there was evidence of a significant first cycle effect with 6 treatment related deaths (5 due to infectious toxicity; 4 in cycle 1 and 1 in cycle 2).[1]
- Close monitoring and consideration of dose reductions is strongly recommended, especially during cycle 1, to avoid

treatment associated complications.

- The incidence of neurotoxicity related to the combination of WBRT and high dose methotrexate is significantly higher in patients aged greater than 60 years, withholding WBRT in the primary setting in these patients should be strongly considered.[2]

Drug status: **Thiotepa:** TGA registered but not PBS listed

Rituximab, cytarabine and **methotrexate** are on the PBS general schedule

Cost: ~ $2,990

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 to 4

Day -5 and 0		
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment
Hydrocortisone	100 mg (IV)	30 minutes before treatment
Rituximab	375 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% as per graded administration rate

Day 1		
Netupitant	300 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with palonosetron)
Palonosetron	0.5 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with netupitant)
Dexamethasone	12 mg (PO)	60 minutes before chemotherapy
Methotrexate	500 mg/m^2 (IV infusion)	in 250 mL sodium chloride 0.9% over 15 minutes
Methotrexate	3,000 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 3 hours

Day 2		
Calcium folinate (Leucovorin)	15 mg/m^2 (IV bolus)	over 1 to 2 minutes. Commence 24 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.
Dexamethasone	8 mg (PO)	ONCE a day with or after food (or in divided doses).
Cytarabine (Ara-C)	2,000 mg/m^2 (IV infusion)	TWICE a day in 500 mL sodium chloride 0.9% over 1 hour (every 12 hours)

Day 3		
Dexamethasone	8 mg (PO)	ONCE a day with or after food (or in divided doses).
Cytarabine (Ara-C)	2,000 mg/m^2 (IV infusion)	TWICE a day in 500 mL sodium chloride 0.9% over 1 hour (every 12 hours)

Day 4		
Dexamethasone	8 mg (PO)	ONCE a day with or after food (or in divided doses).
Thiotepa	30 mg/m^2 (IV infusion)	in 50 mL to 100 mL sodium chloride 0.9% over 30

Day 4		
		minutes

Frequency: 21 days

Cycles: 4

Indications and patient population

Indication:

- Newly diagnosed primary CNS lymphoma (PCNSL) in patients up to 70 years or age with good ECOG status

Caution:

- This protocol may not be suitable for immunodeficient patients such as those with advanced HIV disease. Seek further specialist advice.

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 rituximab. Read more about Hypersensitivity reaction
Premedication	The product information states that premedication is required for this treatment. Please refer to the treatment schedule for suggested premedication regimen. This may be substituted to reflect institutional policy.
Emetogenicity HIGH	Suggested default antiemetics have been added to the treatment schedule, and may be substituted to reflect institutional policy. 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.

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.[3] 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.
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.
Cutaneous effects of thiotepa	Thiotepa is partly excreted though the skin (as sweat) and therefore thiotepa associated skin toxicity is thought to be caused by concentration of thiotepa in the skin. It is therefore important to protect both the patient and health professionals from exposure. Read more about the cutaneous effects of thiotepa
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.
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
Biosimilar drug	Read more about biosimilar drugs on the Biosimilar Awareness Initiative page
Blood tests	FBC, EUC, eGFR, LFTs, LDH at baseline, prior to each treatment and regularly throughout treatment. Methotrexate levels to be monitored every 24 hours until 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:

- Dose modifications are as per the IELSG32 trial protocol unless stated otherwise[4]
- All dose reductions are calculated as a percentage of the starting dose

Age older than 60 years
The incidence of neurotoxicity related to the combination of WBRT and high dose methotrexate is significantly higher in patients aged older than 60 years; withholding WBRT in the primary setting in these patients may be considered.[2]
Consider reducing or omitting cytarabine and thiotepa doses in older patients and/or those with co-morbidities.

Haematological toxicity	
ANC x 10^9/L	
0.5 to less than 1.5	Delay treatment until recovery.
less than 0.5	Delay treatment until recovery and consider reducing cytarabine* dose by 25% for subsequent cycles

Haematological toxicity	
Platelets x 10^9/L	
25 to less than 90	Delay treatment until recovery
less than 25	Delay treatment until recovery and consider reducing cytarabine* and thiotepa doses by 25% for subsequent cycles

* Cytarabine dose reduction is the omission of the 4th dose of the drug (i.e. the 2nd dose on day 3)

Renal impairment*	
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.[5] Methotrexate is contraindicated if CrCl is less than 30 mL/min.	
An increased risk of neurotoxicity has been associated with high dose cytarabine when creatinine clearance is less than 60 mL/min.	
Grade 3 or Grade 4	Delay treatment until recovery and consider reducing cytarabine and thiotepa doses by 25% for subsequent cycles

*IELSG32 trial did not include patients with CrCl less than 60 mL/min[4]

Hepatic impairment	
Hepatic dysfunction[6]	
Mild	No dose modifications necessary
Moderate	No dose modifications necessary
Severe	Withhold treatment, consider alternative therapy

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, cytarabine, and thiotepa by 25%

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

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

Rituximab		
	Interaction	**Clinical management**
Antihypertensives	Additive hypotensive effect	Consider withholding antihypertensive medications 12 hours prior to the rituximab infusion
Immunosuppressants (eg. abatacept and baricitinib etc.)	Increased risk of infection	Concurrent use not recommended. If an immunosuppressant must be used, monitor closely for signs of infection

Thiotepa		
	Interaction	**Clinical management**
CYP2B6 inducers (e.g. phenytoin, phenobarbitone, ritonavir etc.)	Increased toxicity of thiotepa possible due to increased conversion to its active metabolite (tepa)	Avoid combination or monitor for increased toxicity of thiotepa
Drugs metabolised by CYP2B6 (e.g. bupropion, methadone, sertraline, sorafenib etc.)	Increased effect/toxicity of these drugs possible due to inhibition of CYP2B6 by thiotepa resulting in reduced clearance	Avoid combination or monitor for increased effect/toxicity of interacting drugs
Neuromuscular blockers (suxamethonium, pancuronium)	Prolonged apnoea due to inhibition of pseudocholinesterase by thiotepa	Caution advised if general anaesthesia required during or soon after treatment with thiotepa

NK-1 antagonist e.g. aprepitant, fosaprepitant, netupitant		
	Interaction	**Clinical management**
Dexamethasone	Increased effects/toxicity of dexamethasone due to inhibition of its metabolism via CYP3A4	Reduce dose of **antiemetic dexamethasone** by approximately 50% when adding a NK-1 antagonist. For protocols that already recommend a NK-1 antagonist, the dose reduction of **antiemetic dexamethasone** has already been taken into account. If **dexamethasone is part of the chemotherapy protocol**, dose reduction as per the product information is not routinely recommended in clinical practice and no additional dexamethasone is required for antiemetic cover.
Warfarin	Reduced anticoagulant efficacy of warfarin due to increased clearance (aprepitant induces CYP2C9). *Note interaction only applicable to aprepitant/ fosaprepitant	INR should be monitored in the 2 week period, particularly at 7 to 10 days following the administration of aprepitant/ fosaprepitant
Combined oral contraceptive	Reduced contraceptive efficacy due to increased clearance. *Note interaction only applicable to aprepitant/ fosaprepitant	Alternative non-hormonal methods should be used during and for 1 month after stopping aprepitant/ fosaprepitant
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of NK-1 antagonist possible due to increased clearance	Avoid combination or monitor for decreased antiemetic effect. Consider using an alternative antiemetic regimen
CYP3A4 inhibitors (e.g. azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Increased toxicity of NK-1 antagonist possible due to reduced clearance	Avoid combination or monitor for increased adverse effects of NK-1 antagonist (e.g. headache, hiccups, constipation)
Drugs metabolised by CYP3A4 (e.g. etoposide, imatinib, irinotecan, midazolam, paclitaxel, vinblastine, vincristine etc.)	Increased effects/toxicity of these drugs possible due to inhibition of CYP3A4 by NK-1 antagonist	Avoid combination or monitor for increased toxicity especially with orally administered drugs

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 -5 and 0

Approximate treatment time: 4 to 6 hours (initial); 3 to 4 hours (subsequent)

Handling of monoclonal antibodies 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.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Treatment - Time out

Rituximab

Prior to administration:

- check baseline observations
- check for previous adverse events during previous infusions
- verify premedication has been taken. If not, administer 30 to 60 minutes prior to rituximab administration:
  - paracetamol 1000 mg orally AND
  - loratadine 10 mg orally (or similar antihistamine)
  - a steroid may also be included as a premed according to local guidelines

Initial infusion:

- **commence rituximab** infusion at 50 mg/hr for 30 minutes
- repeat observations prior to each rate increase
- **increase rate** by 50 mg/hr every 30 minutes, up to a maximum of 400 mg/hr if observations are stable
- flush with ~ 100 mL of sodium chloride 0.9%

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have completely resolved, recommence the infusion at half the rate prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Transient hypotension may occur. Consider withholding antihypertensive medication for 12 hours before and during infusion.

Subsequent infusions:

If an adverse event was experienced with initial infusion recommence infusion at the same rate as initial infusion

- **commence** rituximab infusion at 100 mg/hr
- repeat observations prior to each rate increase
- increase rate by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~ 100 mL of sodium chloride 0.9%

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have resolved, recommence the infusion at **half the rate** prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Read more about rapid infusion rituximab

Deaccess CVAD.

Day 1

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.

- daily weight
- strict fluid balance
- dipstick urinalysis to monitor pH:
  - prior to treatment
  - on all urine output

Prime IV line(s).

Access CVAD.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Commence corticosteroid eye drops 24 hours before starting cytarabine. Continue for 72 hours after completion of the last dose of cytarabine.

Chemotherapy - Time out

Methotrexate infusion

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.

Note: A large volume of intravenous fluid is 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)

First dose of methotrexate:

Administer via IV infusion over 15 minutes

Note: the starting time of the methotrexate infusion must be documented as the calcium folinate (leucovorin) rescue is to commence exactly 24 hours after the start of the methotrexate and continue until the methotrexate level is less than 0.1 micromol/L

Second dose of methotrexate (to commence immediately after the first dose):

- administer via IV infusion over 3 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

Note: Start calcium folinate (leucovorin) rescue 24 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

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

Days 2 and 3

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.

- daily weight
- strict fluid balance
- dipstick urinalysis to monitor pH:
  - prior to treatment
  - on all urine output

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

Note: Start calcium folinate (leucovorin) rescue 24 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

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%.

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 60 minutes:
- flush with ~50 mL of sodium chloride 0.9%.

Administer second dose of cytarabine 12 hours after first dose.

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

Day 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.

- daily weight
- strict fluid balance
- dipstick urinalysis to monitor pH:
  - prior to treatment
  - on all urine output

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

Thiotepa

- administer via IV infusion over 30 minutes
- use a 0.2 micron in-line filter
- flush with ~ 50 mL of sodium chloride 0.9%
- read more about skin management associated with thiotepa

Deaccess CVAD.

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

Discharge information

Antiemetics

- Antiemetics as prescribed.

Corticosteroid eye drops

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

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)	
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.
Headache	
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
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
Cutaneous effects	Rash, erythema, pruritus and/or hyperpigmentation can occur during treatment with thiotepa. As thiotepa is partially excreted through the skin, it is important to protect both the patient and health professionals from exposure. Read more about the cutaneous effects of thiotepa
Diarrhoea	Read more about treatment induced diarrhoea
Dizziness	Feeling faint or lightheaded, weak or unsteady. Advise patients to stand up slowly from sitting down or lying down positions and increase fluid intake if dehydrated.
Fatigue	Read more about fatigue
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.
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
Palmar-plantar erythrodysaesthesia (PPE) - hand-foot syndrome (HFS)	Bilateral erythema, tenderness, pain, swelling, tingling, numbness, pruritus, dry rash, or moist desquamation and ulceration of the palms and soles. It is also known as hand-foot syndrome (HFS). Symptoms appear to be dose dependent and palms are affected more than soles. Read more about hand-foot syndrome associated with chemotherapy
Photosensitivity	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
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)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
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
Reduced libido and sexual dysfunction	Lowered sexual desire as well as any physical or psychological problem that interferes with the ability to have and/or enjoy sex.

Evidence

The evidence supporting this protocol is provided by a phase 2 multicentre international randomised trial (IELSG32) involving 227 patients who were randomised to one of three regimens; methotrexate/cytarabine, methotrexate/cytarabine/rituximab or methotrexate/cytarabine/thiotepa/rituximab (MATRix) in patients aged 18 to 70 years newly diagnosed primary CNS lymphoma.[4]

Between 2010 and 2014, 75 patients were randomised to receive 4 cycles of methotrexate 3.5 g/m^2 on day 1 plus cytarabine 2 g/m^2 twice daily on days 2 and 3 (group A), 74 patients were randomised to receive 4 cycles of rituximab 375 mg/m^2 on days -5 and 0 plus methotrexate 3.5 g/m^2 on day 1 plus cytarabine 2 g/m^2 twice daily on days 2 and 3 (group B) and 78 patients were randomised to receive 4 cycles of rituximab 375 mg/m^2 on days -5 and 0 plus methotrexate 3.5 g/m^2 on day 1 plus cytarabine 2 g/m^2 twice daily on days 2 and 3 plus thiotepa 30 mg/m^2 on day 4 (group C; MATRix). The three groups repeated treatment every 3 weeks. Autologous peripheral blood stem cells were collected after the second chemotherapy course in patients without progressive disease. Patients with responsive or stable disease after the first stage were then randomly allocated between whole-brain radiation therapy (WBRT) and autologous stem cell transplantation.[7]

Consolidation WBRT (photons of 4–10 MeV; five fractions per week; fraction size 180 cGy) was started within 4 weeks from the last induction course. Whole-brain was irradiated by two opposite lateral fields including the first two cervical vertebrae and the posterior two-thirds of the orbits with 36 Gy, with the addition of a 9 Gy tumour-bed boost in patients in partial response; orbits were shielded after 30 Gy (after 36 Gy in the case of intraocular disease). The conditioning regimen of high-dose chemotherapy supported by ASCT consisted of carmustine 400 mg/m^2 on day –6, and thiotepa 5 mg/kg every 12 hours on days –5 and –4 followed by re-infusion of autologous peripheral blood stem cells.

The primary end point of the first randomisation was centrally assessed complete remission (CR) after induction chemo(immuno)therapy and secondary end points were toxicity, overall survival (OS), relapse rates and neurotoxicity. The primary endpoint of the second randomisation (to whole brain radiation therapy or autologous stem cell transplantation) was the 2-year progression-free survival (PFS).

The expert reference panel supported publication of the protocol on the basis of the information summarised below. The committee was most strongly influenced by the trials by Ferreri et al.[4, 7]

Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
Phase II trials	Ferreri et al. 2016[4]	**Yes**	Yes	-
	Ferreri et al. 2017[7]	**Yes**	Yes	-
Guidelines	**Date published/revised**	**Supports Use**	**Is the dose and regimen consistent with the protocol?**	**Comments**
NCCN	September, 2022	**Yes**	Yes	-
BCCA	N/A	**N/A**	-	-
CCO	August, 2020	**Yes**	Yes	-

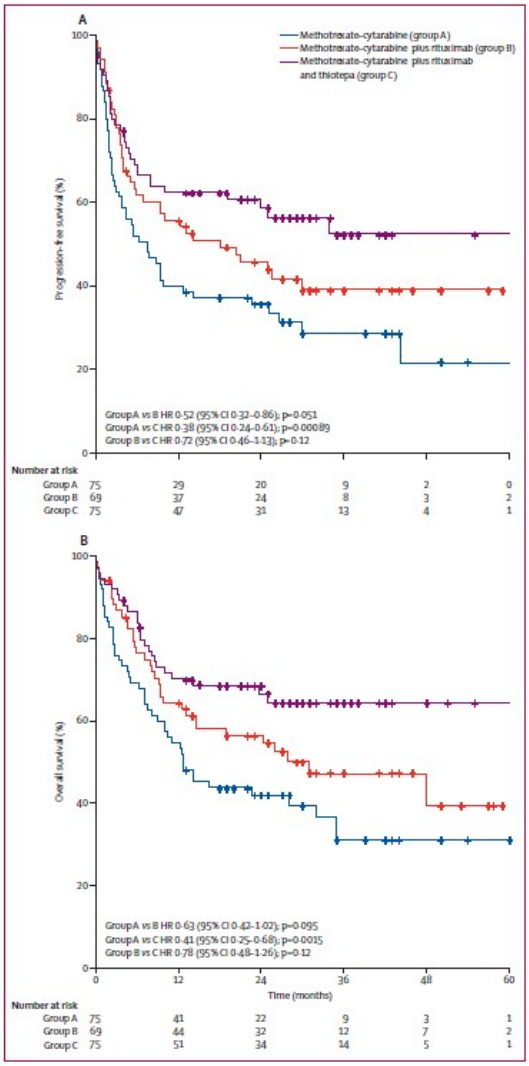
Efficacy

At median follow-up of 30 months patients treated with MATRix had a CR rate of 49% (95% CI 38–60), compared with 23% (14–31) of those treated with methotrexate–cytarabine alone (hazard ratio 0.46, 95% CI 0.28–0.74) and 30% (21–42) of those treated with methotrexate–cytarabine plus rituximab (0.61, 0.40–0.94). Furthermore, 96 (44%) of 219 patients remain progression free: 22 (29%) of 75 in those treated with methotrexate–cytarabine alone, 30 (43%) of 69 with addition of rituximab, and 44 (59%) of 75 with addition of rituximab and thiotepa.[4]

According to the treatment group (figure 1A), the 2-year PFS was 36% (95% CI 31–41) for group A, 46% (40–52) for group B, and 61% (55–67) for group C (MATRix). Overall, 113 (52%) of 219 patients were still alive at a median follow-up of 30 months 27 (36%) of 75 in group A, 36 (52%) of 69 in group B, and 50 (67%) of 75 in group C (MATRix).[4]

The 2-year OS rate was 42% (95% CI 36–48) in group A, 56% (50–62) in group B, and 69% (64–74) in group C (MATRix) (figure 1B).[4]

Figure 1: Survival outcomes (A) Progression-free survival and (B) overall survival curves of registered patients divided according to induction treatment group. Tick marks represent censored patients.[4]



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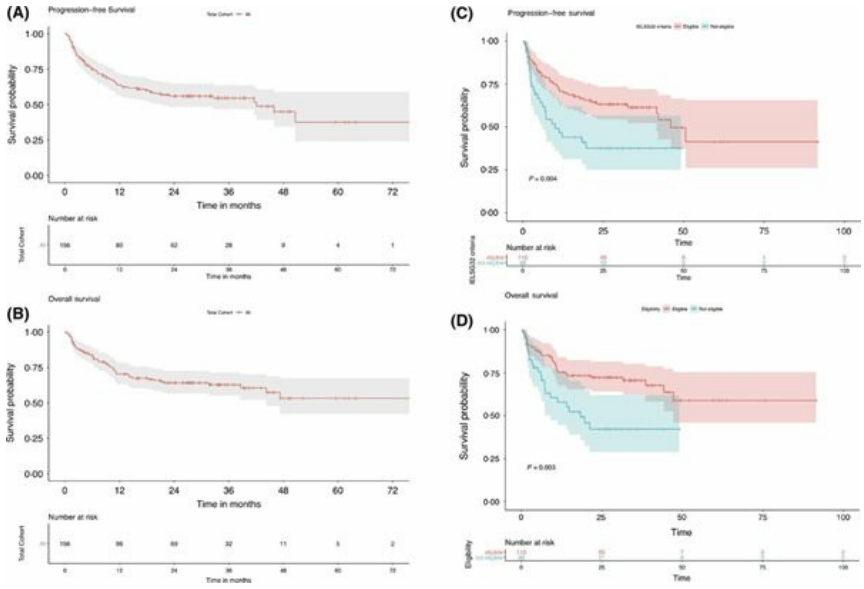
Furthermore, longer term follow-up data from the IELSG32 trial[8] has been published in patients treated with MATRix. At a median follow up of 88 months (~7 years), the OS was found to be 56% (95% CI 52-60), compared with 21% (95% CI 4-47) in patients treated with methotrexate-cytarabine alone (hazard ratio 0.42, 95% CI 0.24-0.64) and 37% (95% CI 26-48) in patients treated with methotrexate-cytarabine plus rituximab (hazard ratio 0.66, 95% CI 0.44-0.98).[8]

In addition, 52% (95% CI 47-57) patients treated with MATRix remained progression free at a median of 88 months. This was significantly higher compared to a PFS of 20% (95% CI 3-48) in those treated with methotrexate-cytarabine alone and 29% (95% CI 13-47) in those treated with methotrexate-cytarabine plus rituximab.[8]

Outside of a clinical trial setting, data on patients receiving MATRix recapitulated similar outcomes. Out of 156 patients treated with MATRix, 79% (n=123, 95% CI 71-85) achieved a response (35% complete response, 44% partial response), 4% (n=6) had stable disease and 10% (n=16) had documented progressive disease. Stem cell mobilisation was performed in 94% of the responders, and majority (67.5%) proceeded to receive consolidation treatment with an autologous stem cell transplant, WBRT or further chemotherapy. The remainder of responders did not receive consolidation due to infectious complications, lowered performance status, co-morbidities or due to decision by the patient and/or treating physician. At a median follow-up of 27.4 months, the overall survival was 64% (100 out of 156) and the median OS was not reached.[9]

Of note, there was a significant improvement in PFS and OS for patients who fulfilled IELSG32 eligibility criteria, compared with those who were included in the series but would have otherwise been ineligible for MATRix in IELSG32 study.[9]

Figure 2: Progression-free survival and overall survival [9]



Toxicity

Table 1: Comparison of treatment toxicity in the three groups[4]

	Methotrexate–cytarabine (group A; n=75): 223 (74%) courses delivered*				Methotrexate–cytarabine plus rituximab (group B; n=69): 236 (86%) courses delivered*				Methotrexate–cytarabine plus rituximab and thiotepa (group C; n=75): 274 (91%) courses delivered*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Neutropenia	12 (5%)	18 (8%)	99 (44%)	0	24 (10%)	15 (6%)	119 (50%)	0	14 (5%)	31 (11%)	153 (56%)	0
Thrombocytopenia	18 (8%)	43 (19%)	116 (52%)	0	27 (11%)	36 (15%)	140 (59%)	0	21 (8%)	27 (10%)	200 (73%)	0
Anaemia	115 (52%)	63 (28%)	9 (4%)	0	124 (53%)	77 (33%)	6 (3%)	0	131 (48%)	116 (42%)	14 (5%)	0
Febrile neutropenia/ infections	11 (5%)	32 (14%)	10 (4%)	6 (3%)	21 (9%)	23 (10%)	7 (3%)	2 (<1%)	18 (7%)	42 (15%)	3 (1%)	0
Hepatotoxicity	71 (32%)	20 (9%)	6 (3%)	0	76 (32%)	25 (11%)	3 (1%)	0	77 (28%)	19 (7%)	1 (<1%)	0
Nephrotoxicity	28 (13%)	3 (1%)	0	0	31 (13%)	4 (2%)	0	0	17 (6%)	2 (<1%)	1 (<1%)	0
Cardiotoxicity	0	0	0	0	0	2 (<1%)	0	0	0	2 (<1%)	1 (<1%)	0
Coagulopathy/deep vein thrombosis (including pulmonary embolism)	2 (1%)	3 (1%)	0	0	3 (1%)	3 (1%)	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)	2 (<1%)
Gastrointestinal	35 (16%)	1 (<1%)	0	0	106 (45%)	5 (2%)	1 (<1%)	0	81 (30%)	9 (3%)	1 (<1%)	0
Mucositis	20 (9%)	3 (1%)	0	0	37 (16%)	2 (<1%)	2 (<1%)	0	45 (16%)	1 (<1%)	0	0
Acute neurotoxicity	28 (13%)	3 (1%)	3 (1%)	0	34 (14%)	4 (2%)	0	0	19 (7%)	6 (2%)	2 (<1%)	0
Hyperglycaemia	0	4 (2%)	0	0	0	0	0	0	0	0	1 (<1%)	0
Sudden death†	..	..	..	1 (<1%)	..	..	..	0	..	..	..	1 (<1%)
Non-lethal interruptions	0	0	2 (<1%)	0	0	0	2 (<1%)	0	0	0	1 (<1%)	0

Adverse events of grade 1–2 occurring in at least 10% of patients and all grade 3–5 events are reported. *Denominator is the planned number of courses. 42 patients in group A, 50 in group B, and 63 in group C received four courses; three, five, and four patients received three courses; 16, 7, and two received two courses; and 14, seven, and six received a single course. Denominators for the different forms of toxicity are the number of delivered courses. Causes of toxic deaths (grade 5 toxicity) were: septic complication (eight), stroke (three), and sudden death (two). No cases of severe reactions during rituximab infusion were reported. †Of unexplained cause.

Grade 4 haematological toxicity was more common in patients in group C (MATRix) than in the other two groups, but infective complications were similar in the three groups (table 1). Grade 4 non-haematological toxicities were rare. 13 (6%) of 219 patients died of toxicity during induction (7 patients in group A, 3 in group B and 3 in group C) (table 1).[4]

Eight patients later died while off therapy and without evidence of disease after 10–14 months of follow-up; the causes of death were infections (two in group B, two in group C), neurological decline (one in group A, one in group B), sudden death (one in group B), and an unknown cause (one in group C).[4]

Table 2: Disease and treatment related events according to induction and consolidation arm[8]

	Total	Arm A ($n = 75$)	Arm B ($n = 69$)	Arm C ($n = 75$)	WBRT[a] ($n = 70$)	ASCT[a] ($n = 60$)	Others[b] ($n = 74$)
Toxic deaths (1st line)	15	7 (9%)	3 (4%)	3 (4%)	0 (0%)	2 (2%)	-
Progressive disease	66	26 (35%)	18 (26%)	13 (17%)	4 (4%)	2 (2%)	3 (4%)
Relapse after response	51	19 (25%)	17 (25%)	15 (20%)	22 (31%)	19 (32%)	10 (14%)
Salvage therapy	75	30 (40%)	22 (32%)	23 (31%)	15 (21%)	18 (30%)	42 (57%)
Second tumors[c]	8	1/38 (3%)	2/47 (4%)	5/59 (8%)	5/67 (7%)	3 (5%)	0 (0%)
Deaths during/after salvage[d]	7	4 (13%)	0 (0%)	3 (13%)	2 (13%)	2 (11%)	3 (4%)
Deaths of lymphoma	96	43 (57%)	32 (46%)	21 (28%)	19 (27%)	16 (27%)	61 (82%)
Deaths in relapse-free patients[e]	14	2/17 (12%)	6/28 (21%)	6/42 (14%)	9/44 (20%)	3/37 (8%)	2/6 (33%)

[a]Actually delivered consolidation regardless of random allocation.
[b]Denominator: all patients who did not receive WBRT or ASCT; patients died of toxicity during first line were excluded.
[c]Denominator: patients who completed the first-line treatment.
[d]Cause of deaths: bacterial septicemia (2), pneumonia, varicella-zoster virus encephalitis, stroke, brain aspergillosis, unknown.
[e]Cause of deaths: infections (4), cognitive decline (3), second tumor (2), car accident (1), unknown (4). Denominator: patients without lymphoma recurrence at the last visit.

The largest series of PCNSL patients treated with MATRix outside of a clinical trial setting found toxicity was most severe in the first cycle of MATRix. Severe complications were mostly due to infections. 6% of patients (10 out of 156) required an intensive care unit admission due to life-threatening infections. Treatment-related mortality during MATRix was observed to be 6% (9 out of 156; 7 during the first cycle), with causes of death including infectious complications, suspected pulmonary embolism and stroke.[9]

Quality of life (QoL) data was not reported in the original publication of this study, however longer term follow-up of IELSG32 trial participants compared neuropsychological and QoL assessments at the time of trial registration to after consolidation treatment with autologous stem cell transplant (ASCT) or WBRT. Although comparable in efficacy as consolidation methods, patients who received MATRix induction followed by WBRT had greater impairments in attentiveness and executive functions, whereas those who underwent consolidation with ASCT experienced improvement in these cognitive functions, as well as memory and quality of life.[8]

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History

Version 5

Date	Summary of changes
20/06/2023	Dose modifications updated and aligned across PCNSL protocols. Version number changed to v.5

Version 4

Date	Summary of changes
04/05/2023	Methotrexate target level updated. Version number changed to v.4

Version 3

Date	Summary of changes
06/08/2020	Dose modifications updated to be inline across PCNSL protocols. Version number increased to v.3.
08/02/2022	PJP prophylaxis clinical information block updated.
11/11/2022	Reviewed by the haematology reference committee. Changes include: • Long term data added to the evidence section • References added to dose modifications • Updated Rituximab PBS status
03/05/2023	Protocol approved and published. For review in 4 years.

Version 2

Date	Summary of changes
09/03/2020	Biosimilar rituximab added to clinical information. Version number changed to v.2
26/03/2020	Dose modification section updated.

Version 1

Date	Summary of changes
24/11/2017	New protocol taken to Haematology Reference Committee meeting.
22/01/2018	New protocol published on eviQ
25/10/2018	Link added to high dose methotrexate-induced toxicity document in clinical information.
10/10/2019	Clinical information updated with PBS expanded indications for G-CSF.

First approved: 24 November 2017
Last reviewed: 3 May 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/3374
26 Nov 2023

Patient information - Primary CNS lymphoma - MATRix (methotrexate, cytarabine, thiotepa, rituximab)

Patient's name:

Your treatment

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

MATRix (methotrexate, cytarabine, thiotepa, rituximab)

This treatment cycle is repeated every 21 days. You will have up to 4 cycles. Once you have finished your chemotherapy, you may be given radiation therapy; your doctor will advise you if this is necessary.

Day	Treatment	How it is given	How long it takes
-5 and 0	**Rituximab** *(ri-TUX-i-mab)*	By a drip into a vein	**1st cycle:** About 4 to 6 hours **Cycles thereafter:** About 3 to 4 hours
1	**Methotrexate** (*Meth-o-TREX-ate*)	By a drip into a vein	About 4 hours
2	**Calcium folinate (Leucovorin)** (*loo-koe-VOR-in*)	By a drip into a vein	About 5 minutes every SIX hours
2 and 3	**Cytarabine** (*sye-TARE-a-been*)	By a drip into a vein	About 60 minutes TWICE a day
4	**Thiotepa** *(thye-oh-TEA-pa)*	By a drip into a vein	About 30 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 • 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.

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)	
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.
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.**
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.**
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.
Skin changes	• Your skin may become dry, red or more sensitive than normal. It may also peel or blister. • You may notice darkening of skin, especially under your arms and around your neck and groin. • These symptoms are caused by the drug thiotepa. • You should have at least 3 or 4 warm baths every day for 15 to 30 minutes, and whenever you sweat or become very warm/hot. • You should begin bathing 3 to 4 hours after your first dose of thiotepa. • Make sure you wear protective clothing when out in the sun. • If your skin feels dry, try using an unscented moisturising cream every day. • Talk to your doctor or nurse about other ways to manage these symptoms.

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.**
Dizziness or feeling light-headed	• You may feel dizzy or light-headed. • These symptoms may be caused by your treatment, or other problems like dehydration. • If you are feeling dehydrated, drink plenty of fluids (unless you are fluid restricted) as this can be a cause of dizziness. • If you are feeling dizzy, try lying down until the dizziness passes. • When you want to get up from a sitting or lying down position, get up slowly to let your body adjust to the new position. • Tell your doctor or nurse if you get any of the symptoms listed above.
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.**

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.**

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.**

Hand-foot syndrome (palmar-plantar erythrodysaesthesia)	• The palms of your hands and soles of your feet may become:
	  ◦ red and hot
	  ◦ swollen
	  ◦ painful and tender
	  ◦ blistered.
	• The skin in the area may also peel.
	• Moisturise your hands and feet daily with sorbolene or aqueous cream.
	• Keep your hands and feet clean and dry.
	• Avoid hot water, instead use lukewarm water to bathe.
	• Avoid direct sunlight.
	• Avoid unnecessary walking, jogging or exercise.
	• Wear cotton socks and avoid tight-fitting shoes.
	• **Tell your doctor or nurse as soon as possible if you notice any skin changes on your hands or feet.**

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.**
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)	
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.**
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.**
Low sex drive	• This treatment lowers the amount of sex hormone in your body. • You may lose interest in sex, or have trouble having sex. • Talk to your doctor or nurse about ways to manage these symptoms.

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.
- 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 more 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.

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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