High dose Methotrexate, high dose Cytarabine, riTUXimab and Thiotepa (MATRix)Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of primary CNS lymphoma	C85	00508a	Methotrexate: Hospital Cytarabine : Hospital riTUXimab: Hospital Thiotepa: Hospital
Treatment of CNS relapse of a high grade systemic lymphoma[i]	C85	00508b	

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment is administered according to the treatment table below.

A cycle may be repeated every 21 days for up to 4 cycles.

Patients with responsive or stable disease may be considered for further treatment with autologous stem cell transplantation or whole-brain radiotherapy

Note:

- Hydration, alkalinisation and folinic acid therapy are required with high dose methotrexate (See Table Below)

Facilities to treat anaphylaxis MUST be present when therapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1, 2	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[2]	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[1,3,4]	Every 21 days
2	Methotrexate	500mg/m^2	IV infusion	100ml 0.9% NaCl over 15min	Every 21 days
2	Methotrexate	3000mg/m^2	IV infusion	500ml 0.9% NaCl over 3 hours	Every 21 days
3	Folinic acid	15mg/m^2	IV infusion	100ml 0.9% NaCl over 10 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 (See Table 1 below for calculation of dose of Folinic acid based on Methotrexate levels)	Every 21 days
3 and 4	Cytarabine	2000mg/m^2 **AM**	IV infusion	250mL 0.9% NaCl over 1 hour	Every 21 days
3 and 4	Cytarabine (Note: There should be a 12 hour interval between cytarabine doses)	2000mg/m^2 **PM**	IV infusion	250mL 0.9% NaCl over 1 hour	Every 21 days
5	Thiotepa	30mg/m^2	IV infusion	[5]100ml 0.9% NaCl over 30min via a 0.22micrometre filter	Every 21 days
When used for priming					
6-14 (9 days)	G-CSF (round to nearest whole syringe)	5mcg/kg			
When not used for priming consider the use of G-CSF 5mcg/kg daily from day 9 onwards until neutrophil recovery (Consultant decision)					

[1]The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Subsequent infusions can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr.
Development of an allergic reaction may require a slower infusion rate. See Hypersensitivity/Infusion reactions under Adverse Effects/Regimen Specific Complications below.
Any deviation from the advised infusion rate should be noted in local policies.

[2]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.

[3]RiTUXimab should be diluted to a final concentration of 1-4mg/ml.

[4] Rapid rate infusion schedule[ii] See NCCP guidance here
If patients did **not** experience a serious infusion related reaction with their first or subsequent infusions of a dose of riTUXimab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions.
Initiate at a rate of 20% of the total dose for the first 30 minutes and then 80% of the dose for the next 60 minutes (total infusion time of 90 minutes).
If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.
Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to riTUXimab, should not be administered the more rapid infusion.

[5]Tepadina®, must be diluted with an appropriate volume of 0.9% NaCl in order to obtain a final thiotepa concentration between 0.5 and 1 mg/ml

[a]**Methotrexate:** See below for suggested hydration, alkalinisation regimen to be followed with methotrexate **or** Refer to local policy
GFR to be calculated prior to administration of methotrexate infusion**.**
Adequate hydration and urine output are essential for the rapid clearance of methotrexate.

- Commence pre-hydration with sodium bicarbonate containing infusions at 125mls/m^2/hr at least 6 hours prior to methotrexate infusion.
- **Hydration** with at least 3L/m^2/24 hours of **IV fluids** throughout treatment is essential until the methotrexate level is <0. 1 micromol/L
- Urine pH should be ≥ 7.0 prior to commencement and during the methotrexate and folinic acid rescue. Check urine pH at regular intervals (6 hourly)
- **Alkalinisation** can be achieved with 50mmol of sodium bicarbonate over 8 hours in 1000ml sodium chloride 0.9%.

(This volume administered for alkalinisation is included in the total volume of hydration.)

- Check urine pH at regular intervals (6 hourly)
- If the target pH is not reached adjust the sodium bicarbonate concentration to maintain the urinary pH ≥ 7.0
- **Potassium** should be supplemented according to the local policy.
- Check **fluid balance** at regular intervals (4 hourly) through each day. (Furosemide may be administered if fluid output falls below 400mls/m^2 in a 4 hour period).
- **Methotrexate levels** must be taken 48 hours, 72 hours, 96 hours and 120 hours as appropriate after commencement of the initial methotrexate infusion (book levels in advance with lab).

Continue alkalinisation, hydration and folinic acid rescue (Table 1) until methotrexate level is <0. 1 micromol/L

Table1: Table for the Calculation of Folinic Acid Rescue on the basis of Methotrexate Levels

Time after starting Methotrexate infusion	Methotrexate Plasma Concentration micromol/L				
	<0.1	**0.1-2**	**2-20**	**20-100**	**>100**
48 hours	No folinic Acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours
72 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
96 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
120 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
If serum creatinine increases by more than 50% above baseline at 24 hours increase folinic acid rescue.					
At time points over 120 hours continue folinic acid as recommended for 120 hours					

ELIGIBILITY:

- Indication as above
- ECOG 0-3 (age 18-65 years)
- ECOG 0-2 (age 66-70 years)
- Cr Cl > 50ml/min recommended before administration of high-dose methotrexate

EXCLUSIONS:

- Hypersensitivity to riTUXimab, methotrexate, cytarabine, thiotepa or any of the excipients

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- ECG and /or ECHO
- Pulmonary Function Tests
- CT-TAP or PET scan
- MRI brain
- Testicular ultrasound
- Bone marrow aspirate and biopsy
- CSF analysis (flow)
- MMSE
- Pregnancy test
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV.
  *Hepatitis B reactivation: See Adverse events/ Regimen specific complications

Regular tests:

- FBC, renal and liver profile
- LDH
- Cardiac function if clinically indicated

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Haematological:

Table 2: Dose modification in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
>1.5	and	>100	100%
<1.5	and/or	<100	Clinical decision

Renal and Hepatic Impairment:

Table 3: Dose modifications in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
RiTUXimab	No dose adjustment necessary		No dose adjustment necessary			
Methotrexate	**Cr Cl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>80	100%	<50	and	<180	100%
	60-80	65%	51-85	or	>180	75%
	45-60	50%	>85	Contraindicated		
	30-45	Clinical Decision	Contraindicated in severe hepatic impairment			
	<30	Contraindicated				
Cytarabine	**Cr Cl (ml/min)**	**Dose**	If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.			
	>60	100%				
	46-60	60%				
	31-45	50%				
	<30	Contraindicated				
Thiotepa	As thiotepa and its metabolites are poorly excreted in the urine, dose modification is not recommended in patients with mild or moderate renal insufficiency. However, caution is recommended		Since thiotepa is mainly metabolized through the liver, caution needs to be exercised when thiotepa is used in patients with preexisting impairment of liver function, especially in those with severe hepatic impairment. Dose modification is not recommended for transient alterations of hepatic parameters			

Table 4: Dose modification schedule of riTUXimab based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Severe infusion related reaction (e.g dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence		Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x -ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate.
Second occurrence	Consider discontinuing treatment	Consider coverage with steroids for those who are not already receiving steroids.
Mild or moderate infusion-related reaction		Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Methotrexate: Moderate **(refer to local policy)**
Cytarabine: Moderate **(refer to local policy)**
riTUXimab: Minimal **(refer to local policy)**
Thiotepa: Moderate **(refer to local policy)**

PREMEDICATIONS:

Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab. Consider the inclusion of a glucocorticoid in patients not receiving glucocorticoid containing chemotherapy.

Table 5: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO
Chlorphenamine	10mg	IV bolus
Hydrocortisone	100mg	IV bolus (60 minutes before riTUXimab)

To prevent a chemical induced conjunctivitis developing with cytarabine, PrednisoLONE eye drops (e.g. Pred Mild)1-2 drops per eye 4 hourly *during waking hours* prior to cytarabine and continuation for up to 5 days post treatment should be considered.

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor**(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy) Consider interactions between methotrexate and co-trimoxazole.**
- **If co-trimoxazole cannot be avoided, cease PJP prophylaxis at least 48 hours prior to methotrexate infusion and recommence upon neutrophil recovery and clearance of methotrexate.**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Patients should be offered fertility advice prior to treatment, because of the possibility of irreversible infertility.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.
- **Myelosuppression**: Cytarabine and thiotepa are potent bone marrow suppressants and patients require close monitoring and appropriate support until count recovery. Patients receiving these drugs must be under close medical supervision

High dose methotrexate:

- Monitoring of methotrexate levels is essential as delayed methotrexate excretion is potentially an emergency situation. Renal function must be evaluated prior to treatment and patients with creatinine clearance less than 50 mL/min should not receive high dose methotrexate. 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.

Cytarabine

- **Neurotoxicity:** This may occur in patients treated with high dose cytarabine. Assess cerebellar function prior to each cytarabine dose. The risk of neurotoxicity is enhanced in the presence of renal impairment. Ensure that dose of cytarabine is adjusted in renal impairment (Ref Table 4).
- **Cytarabine syndrome:** Treatment with cytarabine may cause a 'Cytarabine Syndrome' characterised by flu-like symptoms, fever, skin rash and occasionally chest pain.

Thiotepa:

Cardiac Disorders: Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on thiotepa

- **Cutaneous Effects of Thiotepa:** Thiotepa is partly excreted through 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.

riTUXimab

- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first infusion of riTUXimab. **(Refer to local policy).** RiTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, pruritis, sneezing, cough, fever or faintness.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on riTUXimab.
- **Severe Cytokine Release syndrome:** Usually occurs within 1 to 2 hours of initiating the first infusion. This syndrome may be associated with some features of cytokine release/tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death.
    - Pulmonary interstitial infiltrates or oedema visible on chest x-ray may accompany acute respiratory failure.
    - For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.
- **Infections:** RiTUXimab should not be administered to patients with an active, severe infection. Caution should be exercised when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.
- **Severe Mucocutaneous Reactions**: These include Steven Johnson syndrome and toxic epidermal necrolysis. Discontinue in patients who develop a severe mucocutaneous reaction. The safety of readministration has not been determined.
- **Progressive multifocal leukoencephalopathy (PML)**: Use of riTUXimab may be associated with an increased risk of PML. If a patient develops PML, the dosing of rituximab must be permanently discontinued.
- **Immunisations**:
    - The safety of immunisation with live viral vaccines following riTUXimab therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on riTUXimab.
    - Patients treated with riTUXimab may receive non-live vaccinations

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- Drugs which compromise renal function eg. aminoglycosides and CISplatin can decrease clearance of methotrexate and lead to systemic toxicity.
- Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and penicillins reduces renal clearance of methotrexate and these drugs should be avoided when using high dose methotrexate. Cotrimoxazole and ciprofloxacin also interact**.**
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Fereri et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomization of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haem 2016. 3(5):e217-227.
2. Fereri et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet 2009; 374: 1512–20
3. Cutaneous effects of thiotepa eviQ 1741 v.3 https://www.eviq.org.au/side-effects-documents/1741-cutaneous-effects-of-thiotepa#6565
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network.
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

a. NCCP | RiTUXimab Rapid Infusion Rate Guidance | V1 2017 available at https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/guidance%20on%20rituximab%20rapid%20infusion%20rate.pdf

7. MabThera®Summary of Product Characteristics Accessed March 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf
8. Methotrexate Summary of Product Characteristics Accessed March 2021 . Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-206-006_23092020105544.pdf
9. Cytarabine 100mg/ml Solution for Injection or Infusion. Accessed October 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-200-002_18082021114137.pdf
10. TEPADINA 15 mg powder for concentrate for solution for infusion Accessed October 2020. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001046/WC500090252.pdf

Version	Date	Amendment	Approved By
1	07/11/2018		Dr Kamal Fadalla, Prof Maccon Keane
2	04/06/2019	Clarification of methotrexate monitoring levels	Dr Kamal Fadalla, Prof M Keane
3	16/09/2021 29/09/2021	Regimen review Updated wording regarding management of hepatitis B reactivation Updated emetogenic potential Updated adverse events/regimen specific complications with regards to riTUXimab and updated recommendations on monitoring for myelosuppression	Dr Kamal Fadalla, Prof M Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for this regimen in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy

[ii] The rapid infusion is an unlicensed means of administration of riTUXimab for the indications described above, in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.