riTUXimab - Methotrexate and Cytarabine Therapy (MCL) - Hyper CVAD Part B

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with mantle cell lymphoma	C83	00467a	Hospital

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 as described in the treatment table below.

Note: Hydration, alkalinisation and folinic acid therapy required with high dose methotrexate (See Treatment Table Below)

Treatment with R-Methotrexate Cytarabine (cycle 2, 4, 6, 8) alternates every 21 days with treatment with R-HyperCVAD (cycle 1, 3, 5, 7) for 8 cycles or until disease progression or unacceptable toxicity develops.

*See NCCP Regimen 00466 riTUXimab Hyper-CVAD Therapy (MCL)-Part A for details.

Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
R-HyperCVAD	R-MA	R-HyperCVAD	R-MA	R-HyperCVAD	R-MA	R-HyperCVAD	R-MA

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent and Rate
1	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr
2	Methotrexate[2]	200mg/m^2	IV infusion	500ml 0.9% NaCl over 2 hours
2	Methotrexate	800mg/m^2	IV infusion	1000ml 0.9% NaCl over 22 hours
3	Folinic Acid	15mg/m^2	IV infusion	100ml 0.9% NaCl over 10 minutes. Begins 36 hours from start of 1st methotrexate and administer every 3 hours until 48 hours post. Then administer according to folinic acid rescue Table 2 below
3,4	Cytarabine[3]	3000mg/m^2 **AM**	IV infusion	500ml 0.9% NaCl over 2 hours
3,4	Cytarabine[3]	3000mg/m^2 **PM** (Note: There should be a 12 hour interval between cytarabine doses)	IV infusion	500ml 0.9% NaCl over 2 hours
6 onwards	G-CSF	5mcg/kg (round to nearest whole syringe)	SC	Daily injection until ANC>1 x 10^9/L for two consecutive days

[1]See table 1: Guidance for administration of riTUXimab.

[2]**Methotrexate**:
Hydration and Alkalinisation regimens are required with methotrexate. See below for **suggested 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

Continue alkalinisation, hydration and folinic acid rescue (Table 2) until methotrexate level is <0. 1 micromol/L

[3] Patients > 60 years of age should receive cytarabine 1000mg/m^2 BD

Table 1: Guidance for administration of riTUXimab

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.
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
riTUXimab should be diluted to a final concentration of 1-4mg/ml.
Rapid rate infusion schedule[i] 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.

Table 2: 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 status 0-2
- LVEF ≥ 50%

EXCLUSIONS:

- Hypersensitivity to riTUXimab, methotrexate, cytarabine or any of the excipients
- Breast feeding
- Pregnancy

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Uric acid
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV
  *Hepatitis B reactivation: See adverse events/ Regimen specific complications

Regular tests:

- FBC, renal and liver profile prior to each cycle and daily until recovery

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

Cytarabine

- The dose of **cytarabine** is reduced to 1000mg/m^2 where:
  - Patients age is greater than 60 years
  - Patients where serum creatinine is greater than 1.5mg/dL or 132.6micromol/L

Methotrexate

- Dose of **methotrexate** is reduced by 50% for patients with an initial serum creatinine level > 1.5mg/dL **or** 132.6micromol /L.
- Dose of methotrexate reduced by 25 to 50% for delayed excretion, nephrotoxicity or grade 3 mucositis with prior courses.

Haematological:

Table 3: Haematological Criteria for administration of R-Methotrexate Cytarabine regimen

ANC (x 10^9/L)		Platelets (x 10^9/L)	
>1*	and	60*	Cycle proceeds. Alternates with riTUXimab-Hyper CVAD Regimen (NCCP Regimen 00466)

*G-CSF has been discontinued for at least 24 hours

Renal and Hepatic Impairment:

Table 4: Dose modifications based on renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
riTUXimab	Probably no dose reduction necessary		Probably no dose reduction necessary			
Methotrexate	**GFR (mls/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>80	100%	<50	and	<180	100%
	60-80	65%	51-85	or	>180	75%
	30-60	50%	>85	Contra-indicated		
	<30	Contra-indicated	Contra-indicated in severe hepatic impairment			
Cytarabine (High dose 1-3g/m²)	**GFR (mls/min)**	**Dose**	If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.			
	>60	100%				
	45-60	60%				
	31-45	50%				
	<30	omit				

Management of adverse events:

Table 5: 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:

riTUXimab: Minimal **(Refer to local policy)**
Methotrexate: Moderate **(Refer to local policy)**
Cytarabine: 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 6: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60 minutes prior to riTUXimab infusion
Chlorphenamine	10mg	IV bolus 60 minutes prior to riTUXimab infusion
Hydrocortisone	100mg	IV bolus 60 minutes prior to riTUXimab infusion

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). Hold prior to administration of Methotrexate**
- PJP prophylaxis **(Refer to local policy). Omit co-trimoxazole administration with high dose methotrexate. Co-trimoxazole should be discontinued at least 1 week prior to methotrexate**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Mouth care **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **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.
- **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.
- **Myelosuppression:** Cytarabine is a potent bone marrow suppressant. Patients receiving this drug must be under close medical supervision.
- **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, skin rash and occasionally chest pain.
- **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.

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensive 12 hours before and during rituximab infusion.
- Drugs which compromise renal function can decrease clearance of methotrexate and lead to systemic toxicity. Avoid concurrent use of NSAIDs and sulphonamides. Large doses of penicillin may also interfere with active renal tubular secretion of methotrexate.
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3A4 inhibitors/inducers**.**

REFERENCES:

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Version	Date	Amendment	Approved By
1	24/01/2019		Dr Anne Fortune
2	04/06/2019	Clarification of methotrexate monitoring levels	Prof E Vandenberghe
3	14/05/2020	Clarification on timing of the administration of cytarabine	Dr Anne Fortune
4	27/04/2021	Reviewed. Updated emetogenic potential and adverse effects (hepatitis B reactivation).	Dr Anne Fortune

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 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.