riTUXimab-HyperCVAD Therapy (MCL) – Part A

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with mantle cell lymphoma	C83	00466a	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.
Treatment with R-HyperCVAD (Part A) (cycle 1, 3, 5, 7) is alternated every 21 days with treatment with R-Methotrexate Cytarabine (Part B)* (cycle 2, 4, 6, 8) for a total of 8 cycles or until disease progression or unacceptable toxicity develops.
*See NCCP Regimen 00467 R-Methotrexate Cytarabine Therapy (MCL)-Part B 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	Methotrexate	12.5mg	Intrathecal[1]	
2,3,4,5, 12,13,14,15	Dexamethasone	40mg	PO or IV	
2	riTUXimab	375mg/m^2	IV infusion[2] Observe post infusion[2]	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[2,]
2,3,4	Mesna	250mg/m^2	IV bolus	Immediately before the **AM** dose of cyclophosphamide infusion
2,3,4	Cyclophosphamide	300mg/m^2 **(AM Dose)**	IV infusion	500ml 0.9% NaCl over 3 hours
2,3,4	Mesna	250mg/m^2	IV bolus	3 hours after the start of **AM** dose of cyclophosphamide infusion
2,3,4	Mesna	250mg/m^2	IV bolus	Immediately before the **PM** dose of cyclophosphamide infusion
2,3,4	Cyclophosphamide	300mg/m^2 **(PM Dose)** To start 12 hours after start of AM dose	IV infusion	500ml 0.9% NaCl over 3 hours
2,3,4	Mesna	250mg/m^2	IV bolus	3 hours after the start of **PM** dose of cyclophosphamide infusion

5, 12	vinCRIStine[3] (max 2mg)	1.4mg/m^2	IV infusion	50ml 0.9% NaCl over 15min
5	DOXOrubicin[4]	50mg/m^2	IV infusion	1000ml 0.9% NaCl over 24 hours (**PM dose** start 12 hours after end of last cyclophosphamide infusion)
7 onwards	G-CSF (round to nearest whole syringe)	5mcg/kg	sc	Until ANC>1 x 10^9/L for 2 consecutive days
[1]Refer to NCCP Guidance on the Safe Use of Intrathecal Chemotherapy in the Treatment of Cancer https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/itcguidance.pdf				
[2]See table 1:Guidance for administration of rituximab.				
[3]vinCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer. https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf				
[4]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2 **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] and to the age of the patient.**				

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[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.

ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- LVEF ≥ 50%
    - Where a patient's LVEF <50%, consideration could be given to the administration of doxorubicin over 48 hours at the discretion of the treating consultant.

EXCLUSIONS:

- Hypersensitivity to riTUXimab, cyclophosphamide, DOXOrubicin, vinCRIStine, 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
- ECG
- Cardiac function using MUGA or ECHO (LVEF ≥50% to administer DOXOrubicin)
- 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 as clinically indicated
- Assessment of peripheral neuropathy status prior to each cycle
- 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
- Note: Patients may have their first dose of riTUXimab delayed or omitted at the discretion of the prescribing Consultant if there is concern for tumour lysis syndrome or cytokine release syndrome.

Haematological:

Table 1: Haematological criteria for administration of R-Hyper-CVAD

ANC (x 10^9/L)		Platelets (x 10^9/L)	
>1*	and	60*	Cycle proceeds. Alternates with riTUXimab-Methotrexate Cytarabine Therapy (MCL) Part B (NCCP Regimen 00467)

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

Renal and Hepatic Impairment:

Table 2: Recommended dose modifications based on renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
riTUXimab	Probably no dose reduction necessary		Probably no dose reduction necessary			
DOXOrubicin	No dose reduction required. Clinical decision in severe renal impairment		**Bilirubin (micromol/L)**	**Dose**		
			20-51	50%		
			51-85	25%		
			>85	omit		
			If AST 2-3 x normal, give 75% dose. If AST >3x ULN, give 50% dose.			
Cyclophosphamide	**CrCl (ml/min)**	**Dose**	Severe impairment: Clinical Decision			
	>20	100%				
	10-20	75%				
	<10	50%				
vinCRIStine	No dose reduction required		**Bilirubin (micromol/L)**		**AST/ALT (Units)**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit

Neurotoxicity:

Table 3: Recommended dose modification of vincristine based on neurotoxicity (CTCAE v 4.0)

Symptom	Dose of Vincristine
Grade 1	100%
Grade 2	Hold until recovery, then reduce dose by 50 %
Grade 3,4	Omit

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:

riTUXimab: Minimal **(Refer to local policy)**
DOXOrubicin: Moderate **(Refer to local policy)**
Cyclophosphamide: Moderate **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**

PREMEDICATIONS:

Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab.

Table 5: 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
Ensure glucocorticoid component of the treatment regimen (Dexamethasone 40mg) is given at least 30 minutes prior to riTUXimab infusion		

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor **(Refer to local policy). If a PPI is used it should be held before the administration of methotrexate.**
- PJP prophylaxis **(Refer to local policy) If co-trimoxazole is used it needs to be discontinued at least one week prior to commencing (riTUXimab-Methotrexate-Cytarabine (Part B) cycle NCCP Regimen 00467a)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis. Avoid the concurrent use of azoles and vinCRIStine (5) **(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.

- **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 Toxicity:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on riTUXimab**.** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with cardiac dysfunction.
- **Neuropathy:** vinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to

receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months. A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.

- **Extravasation**: DOXOrubicin and vinCRIStine cause pain and possible tissue necrosis if extravasated (**Refer to local policy**).
- **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.
- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-FU, cyclophosphamide or paclitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3A4 inhibitors / inducers**.**

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Version	Date	Amendment	Approved By
1	24/01/2019		Dr Anne Fortune
2	27/04/2021	Updated recommendation for dose modification in hepatic impairment (cyclophosphamide), amended emetogenic potential and updated adverse effects (hepatitis B reactivation).	Dr Anne Fortune

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.
Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient

[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.