riTUXimab, Methotrexate, Procarbazine and vinCRIStine (R-MPV) – 14 Days Induction Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of newly diagnosed primary CNS lymphoma (PCNSL)	C85	00664a	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 once every 14 days for 5 to 7 cycles.

- Patients who fail to achieve a complete response (CR) after 5 cycles can be considered for two additional cycles of R-MPV.
- Patients should be considered for radiotherapy or stem cell transplantation after chemotherapy.
- After chemo-radiotherapy or chemotherapy, patients should be considered for two cycles of consolidation high-dose cytarabine.
- Patients with malignant cytology from cerebrospinal fluid (CSF) or high risk of leptomeningeal disease should be considered for intrathecal methotrexate between cycles of high dose IV methotrexate.
- Patients with lymphoma outside of the CNS should be considered for additional cytotoxic treatment in parallel to this regimen.

Please Refer to NCCP Regimen 00666 High Dose Cytarabine Consolidation Therapy (post R-MPV) which is used after riTUXimab, Methotrexate, Procarbazine and vinCRIStine (R-MPV) – 14 Days Induction Therapy

Note:

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

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1 to 7	Procarbazine[1]	100mg/m^2 ONCE a day	PO	N/A	**Cycles 1, 3, 5 and 7 only**
2	1	riTUXimab[2]	500mg/m^2	IV infusion[3] Observe post infusion	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[3]	Every 14 days
3	2	vinCRIStine[4]	1.4mg/m^2 (max 2mg)	IV infusion	50ml 0.9% NaCl over 10min	Every 14 days
4	2	Methotrexate[5]	3,500mg/m^2	IV infusion	500ml 0.9% NaCl over 2 hours	Every 14 days
5	3	Folinic Acid (Calcium leucovorin)	15mg/m^2 every 6 hours	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 <0.04 micromol/L (See Table 2 below for calculation of dose of Folinic acid based on methotrexate levels)	Every 14 days

[1] Procarbazine is available as 50mg capsules, round dose to nearest 50mg.

[2] Consideration can be given to the administration of riTUXimab on Day 2 if more suitable for certain patients.

[3] See Table 1: Guidance for administration of riTUXimab.

[4] 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

[5] **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.
  - Alkalinisation can be achieved with 50mmol of sodium bicarbonate over 8 hours in 1000ml sodium chloride 0.9%.
- **Hydration** with at least 3L/m^2/24 hours of **IV fluids** throughout treatment is essential until the methotrexate level is <0.04 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).

(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 or weight gain of >1kg from baseline or positive fluid balance of >1L).
- **Methotrexate levels** must be taken every 24 hours as appropriate after commencement of the initial methotrexate infusion (book levels in advance with lab) until clearance of methotrexate.

Continue alkalinisation, hydration and folinic acid rescue (Table 2) until methotrexate level is <0.04 micromol/L.

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.

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				
	<0.04	**0.04-2**	**2-20**	**20-100**	**>100**
48 hours	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	20mg/m^2 every 6 hours	200mg/m^2 every 6 hours
72 hours	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	20mg/m^2 every 6 hours	200mg/m^2 every 6 hours	2000mg/m^2 every 6 hours
96 hours	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	20mg/m^2 every 6 hours	200mg/m^2 every 6 hours	2000mg/m^2 every 6 hours
120 hours	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	20mg/m^2 every 6 hours	200mg/m^2 every 6 hours	2000mg/m^2 every 6 hours
Folinic acid rescue should continue for at least 72 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.					
Once the folinic acid dose has been escalated, the dose should not be de-escalated according to response.					

Note:
This table is a recommendation based on the agreed methotrexate target levels for this regimen. Different tables and methotrexate target levels may be employed locally due to different practice and methotrexate serum monitoring.

ELIGIBILITY:

- Indications as above
- CrCl must be >80ml/min prior to receiving full dose high dose MTX and is contra-indicated in CrCl <30ml/min. Refer to dose modifications section.

CAUTION:

- Use with caution in patients with pre-existing immunodeficiency
- The incidence of neurotoxicity related to the combination of radiotherapy and high dose methotrexate is significantly higher in patients aged older than 60 years.

EXCLUSIONS:

- Hypersensitivity to riTUXimab, methotrexate, vinCRIStine, procarbazine or any of the excipients

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist or Consultant Haematologist working in the area of haematological malignancies. Treatment should be given in a specialist inpatient unit with appropriate expertise in high dose methotrexate.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- ECG and/or ECHO
- Ophthalmologic examination to assess for ocular involvement
- Lumbar puncture with CSF for immunophenotyping
- MRI Brain and Spine
- PET CT to include Brain
- CT chest abdomen and pelvis or PET/CT
- Bone marrow aspirate and biopsy
- Pregnancy test as applicable
- 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
- LDH

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.
- Dose reductions of methotrexate should be considered in patients who have persistently high methotrexate levels, renal impairment or severe toxicity from methotrexate in the prior cycle.

Haematological:

Table 3: Dose modification in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1.0	and	≥100	100%
<1.0	And/or	<100	Clinical decision

Renal and Hepatic Impairment:

Table 4: Dose modification 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				
vinCRIStine	No dose adjustment necessary		**Bilirubin (micromol/L)**		**AST/ALT**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit
Procarbazine	**Serum creatinine**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>177 micromol/L	50%	>50			Consider a dose reduction
	Severe renal impairment	Not recommended	>85	or	>180	Contra-indicated

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.

Table 6: Dose modification of vinCRIStine based on neurotoxicity* (CTCAE v4.0)

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

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

riTUXimab: Minimal **(Refer to local policy)**
Methotrexate: Moderate **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**
Procarbazine: Moderate to High **(Refer to local policy)**

Note:
Consideration should be given to classifying this regimen as moderately emetogenic.

Patients may be at increased risk of PJP due to receipt of high dose steroids prior to initiation of R-MPV; dexamethasone should be discontinued or omitted post methotrexate.
It is recommended that oral aprepitant (+ 5-HT3 receptor antagonist) is used post treatment in place of dexamethasone.

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 7: 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)

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy).**
- PJP prophylaxis **(Refer to local policy). Consider interactions between methotrexate and co-trimoxazole.**
    - Due to treatment intensity, an alternative PJP prophylaxis to co-trimoxazole could be considered at the discretion of the primary consultant.
    - **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.**
- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy).**
- G-CSF prophylaxis for 3 to 5 days after each cycle **(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.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.

riTUXimab

- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first infusion **(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, hyperphosphataemia, 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 normalised.
- **Severe Mucocutaneous Reactions:** These include Stevens-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. Patients must be monitored for any new or worsening neurological symptoms. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of riTUXimab must be permanently discontinued.
- **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 which may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.
- **Vaccines:** 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 or whilst peripherally B cell depleted. Patients treated with riTUXimab may receive non-live vaccinations.

Methotrexate

- **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. 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.

vinCRIStine

- **Peripheral 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.
- **Extravasation:** vinCRIStine causes pain and possible tissue necrosis if extravasated (Refer to local policy).
- **Procarbazine Allergic skin reactions**: Treatment should be interrupted on the appearance of allergic skin reactions.

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensive 12 hours before and during rituximab infusion.
- 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**.**
- Procarbazine is a weak MAO inhibitor and therefore interactions with certain foodstuffs and drugs, although very rare, must be borne in mind. Thus, owing to possible potentiation of the effect of barbiturates, narcotic analgesics (especially pethidine), drugs with anticholinergic effects (including phenothiazine derivatives and tricyclic antidepressants), other central nervous system depressants (including anaesthetic agents) and anti-hypertensive agents, these drugs should be given concurrently with caution and in low doses.
- Intolerance to alcohol (Disulfiram-like reaction) may occur with procarbazine.
- Concurrent administration of vinCRIStine with allopurinol, pyridoxine or isoniazid may increase the incidence of cytotoxic induced bone marrow depression.
- CYP 3A4 enzyme inducers may increase the clearance of vinCRIStine. CYP3A4 enzyme inhibitors may decrease the clearance of vinCRIStine.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	01/12/2022		Prof Patrick G Morris, Dr Liam Smyth

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication 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 aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication 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.