R-IVAC Therapy
(Patients less than or equal to 65 years)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with extensive stage Burkitt Lymphoma aged less than or equal to 65 years	C83	00399a	Hospital

TREATMENT:

The starting dose of the drugs detailed may be adjusted downward by the prescribing clinician, using their medical judgement, to consider a patient's specific clinical circumstances.

Treatment is administered as described in the treatment table below.

Treatment with R-IVAC for patients aged less than or equal to 65 years alternates with R-CODOX-M Therapy for patients aged less than or equal to 65 years (Ref NCCP regimen 00398) for 4 cycles (2 cycles of R-CODOX-M and 2 cycles of R-IVAC are administered in total).

Note:

- **Hydration therapy required for safe administration of ifosfamide (See Table below)**
- Each cycle of R-IVAC should commence on the first day after R-CODOX-M that the unsupported absolute neutrophil count (ANC) is > $1x10^9$/L and platelet count is >$75x10^9$/L

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

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
0	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[2]	500ml 0.9% NaCl at a maximum rate of 400mg/hr[1,3,4]
1-5	Etoposide	60mg/m^2	IV infusion	500ml 0.9% NaCl over 1 hour
1-5	[5]Ifosfamide	1500mg/m^2	IV infusion	1000ml 0.9% NaCl over 2 hours
1-5	Mesna	800mg/m^2	IV Bolus	10-15 minutes before start of ifosfamide infusion
1-5	Mesna	800mg/m^2	IV Bolus	4 hours after start of ifosfamide infusion
1-5	Mesna	800mg/m^2	IV Bolus	8 hours after start of ifosfamide infusion
1, 2	Cytarabine	2000mg/m^2 **AM**	IV infusion	500ml 0.9% NaCl over 3 hours
1, 2	Cytarabine (Note: There should be a 12 hour interval between cytarabine doses)	2000mg/m^2 **PM**	IV infusion	500ml 0.9% NaCl over 3 hours.
7 onwards	G-CSF (Round to nearest whole syringe)	5micrograms/kg	SC	Daily injection until ANC >1x10^9/L for 2 consecutive days

See Note on Intrathecal Therapy Below

[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[1] 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]**Ifosfamide: Suggested Hydration therapy. (Refer to local policy or see suggested hydration below).**
Ensure IV hydration 1L NaCL 0.9% IV every 6 hours) is given, commencing prior to first dose of ifosfamide and continuing for 24 hours after the ifosfamide has stopped.
Furosemide should also be administered if required to ensure a urinary output of at least 100ml/hour
Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mls or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide

Intrathecal (IT) Therapy

- Patients without CNS involvement should receive standard intrathecal therapy (see Table 1 below)
- Patients with proven or suspected CNS disease should receive intensified intrathecal treatment during the first cycle of R-IVAC /R-CODOX –M (see Table 2 below).
- If CNS disease has cleared after the first cycles of chemotherapy, patients should receive standard IT therapy with subsequent cycles of R-IVAC or R-CODOX-M (Ref NCCP Regimen 00398 R-CODOX-M Therapy (Patients less than or equal to 65 years)).

Table 1: Standard Intrathecal therapy for patients without CNS disease

Day	Drug	Dose	Route and Method of Administration
6*	Methotrexate	12.5mg	Intrathecal injection
7	Folinic Acid	15mg	PO To be taken 24 hours after Intrathecal methotrexate
*Timing of Intrathecal therapy can be moved +/- 3 days as per local policy 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			

Table 2: Intensified Intrathecal therapy for patients with proven or suspected CNS disease

Day	Drug	Intrathecal Dose
5	Methotrexate	12.5mg
6	Folinic Acid	15mg PO to be taken 24 hours after Intrathecal methotrexate
7,9	Cytarabine	70mg
Timing of Intrathecal therapy can be moved +/- 3 days as per local policy. 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		

ELIGIBILITY:

- Indication as above

EXCLUSIONS:

- Hypersensitivity to etoposide, ifosfamide, cytarabine, riTUXimab 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.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- ECHO or MUGA scan if clinically indicated
- 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
- Assess neurological function daily while on ifosfamide
- Check urinalysis for haematuria prior to ifosfamide and daily during treatment with ifosfamide
- 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 3: Haematological Requirements prior to each cycle

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
>1	and	>75	100% Dose

Renal and Hepatic Impairment:

Table 4: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
riTUXimab	**No dose adjustment necessary**		**No dose adjustment necessary**			
Ifosfamide	**CrCl (ml/min)**	**Dose**	Mild and moderate: no dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy. Dose reductions are probably not necessary for patients with altered liver function. However ifosfamide is extensively hepatically metabolised and some clinicians recommend a 25% dose reduction for patients with significant hepatic dysfunction (serum AST > 300units/L or bilirubin > 51.3 micromol/L. Clinical decision.			
	>60	100%				
	40-59	70%				
	<40	Clinical Decision				
Etoposide	**CrCl (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**		**AST**	**Dose**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical response					
Cytarabine High Dose 1-3g/m^2	**CrCl (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	CI				

Other Toxicity:

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).**
Etoposide Low **(Refer to local policy).**
Ifosfamide Moderate **(Refer to local policy).**
Note: High emetogenic potential may be considered as a result of cumulative effect over 5 days of treatment
Cytarabine Moderate **(Refer to local policy).**
Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.

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)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(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.
Please refer to NCCP Regimen 00542 Rituximab 375mg/m^2 Combination Therapy-21 day for detailed information on adverse effects/regimen specific complications to this regimen.

- **Ifosfamide-induced encephalopathy**: This may occur in patients treated with ifosfamide.
  - Consider risk factors for ifosfamide induced encephalopathy (renal insufficiency, low serum albumin, large pelvic mass).

  - Methylene blue is used to manage ifosfamide-associated encephalopathy **(Refer to local policy)**
- **Renal and urothelial toxicity:** Ifosfamide is both nephrotoxic and urotoxic. Urinalysis should be performed daily to exclude haematuria. For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna. Ifosfamide should be used with caution, in patients with active urinary tract infections**.**
- **Myelosuppression**: Cytarabine is a potent bone marrow suppressant. Patients receiving this drug must be under close medical supervision.
- **Neurotoxicity: T**his 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.
- **Precautions for Intrathecal Administration:** 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**

DRUG INTERACTIONS:

- Avoid concurrent use of ifosfamide with nephrotoxic drugs (e.g. aminoglycosides, NSAIDS) due to additive nephrotoxicity.
- Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.
- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- There is a diminished response to vaccines and increased risk of infection with live vaccines. Vaccination with live virus vaccines is not recommended for patients on riTUXimab therapy.
- Current drug interaction databases should be consulted for more information eg interaction potential with CYP3A4 inhibitors/ inducers.

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Version	Date	Amendment	Approved By
1	15/11/2017		Prof E Vandenberghe Prof M Keane
2	11/11/2020	Regimen review. Standardisation of treatment table and premedications. Update of adverse events with regard to management of hepatitis B reactivation	Prof E Vandenberghe
3	25/08/2022	Updated renal and hepatic section. Updated emetogenic potential section	Prof M Keane

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.