(R*)- ESHAP Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of relapsed Non Hodgkin Lymphoma	C85	00394a	Hospital
Treatment of relapsed Hodgkins Lymphoma	C81	00394b	Hospital

* riTUXimab to be included in all CD20 positive patients

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 with R**-ESHAP can be repeated at 21 day intervals depending on myelosuppression for 2 cycles pre-transplant. Treatment may be continued for up to 6 cycles in patients not eligible for transplant.

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

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1-5	Methylprednisolone	500mg	IV infusion	100ml 0.9% NaCl over 30mins
1	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]
1-4	Etoposide	40mg/m^2	IV infusion	500ml 0.9% NaCl over 1 hour
1-4	[5]CISplatin	25mg/m^2	IV infusion	1000ml 0.9% NaCl over 24 hours
5	Cytarabine	2000mg/m^2	IV infusion	1000mls 0.9% NaCl over 2 hours
From day 6 onwards	[6]G-CSF	5mcg/kg	SC (Round to nearest whole syringe)	Continued until ANC >1x10^9/L for 2 consecutive days

[1]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 400mg/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 400mg/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[i]
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]Pre hydration therapy required for CISplatin
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above

[6]G-CSF support is required with this regimen (**Refer to local policy or see Suggested support above**)

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to CISplatin, etoposide, cytarabine or any of the excipients.
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus

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, Urate
- Audiology and creatinine clearance if clinically indicated
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile
- LDH prior to each cycle
- Regular glucose monitoring while receiving steroid therapy-urinalysis 2-4 times/day
  If glucose detected in urinalysis, monitor blood glucose daily

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

Renal and Hepatic Impairment:

Table 1: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
CISplatin	**CrCl (ml/min)**	**Dose**	No dose modification required			
	>60	100%				
	45-60	75%				
	<45	consider carboplatin				
Etoposide	**Cr Cl (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	**CrCl (ml/min)**	**Dose**	If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.			
	>60	100%				
	45-60	60%				
	30-45	50%				
	<30	Avoid				

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (**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 2: 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 Methylprednisolone is given at least 30 minutes prior to riTUXimab infusion		

- Hydration prior to CISplatin administration **(Refer to local policy or see recommendations above)**
- 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 continued 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)**
- 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.

- **Myelosuppression:** Cytarabine is a potent bone marrow suppressant. Patients receiving this drug must be under close medical supervision and,should have leucocyte and platelet counts performed daily
- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle of CISplatin
- **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 1).
- **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.
- Please Refer to **NCCP regimen 00208 RiTUXimab Monotherapy** for detailed information on adverse reactions/Regimen Specific Complications associated with RiTUXimab Therapy

DRUG INTERACTIONS:

- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CISplatin	L01XA01
Etoposide	L01CB01
Cytarabine	L01BC01

REFERENCES:

1. Velasquez WS. et al. ESHAP- An effective chemotherapy regimen in Refractory and Relapsing Lymphoma: A 4-year Follow up Study. J Clin Oncol 1994;12, (6):1169-1176.
2. Aparicio J, Segura A. et al. ESHAP is an active regimen for relapsing Hodgkin's disease. Ann Oncol. 1999;10(5):593.
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf

4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
5. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed May 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-081-001_13022020153905.pdf
6. Etoposide Summary of Product Characteristics Accessed May 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_29072019103821.pdf
7. Cytarabine 100mg/ml Solution for Injection or Infusion. Accessed May 2020 Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-082-001_18102019163721.pdfhttp://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1390-091-001_09122014091042.pdf

Version	Date	Amendment	Approved By
1	09/03/2018		Prof Elisabeth Vandeberghe
2	12/11/2020	Regimen review. Standardisation of treatment table and premedications. Update of adverse events with regard to management of hepatitis B reactivation	Prof Elisabeth Vandeberghe

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.