(R*)-DHAP Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of relapsed Non Hodgkin Lymphoma*	C85	00395a	Hospital
Treatment of relapsed Hodgkins Lymphoma	C81	00395b	Hospital

* riTUXimab to be included in CD20 positive patients

TREATMENT:

The starting dose of the drugs detailed above may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

CISplatin is administered on Day 1 and cytarabine is administered twice daily on day 2. Treatment is repeated at 21 day intervals for up to 6 cycles.
If DHAP is being used prior to autologous SCT, peripheral blood stem cell harvesting is usually performed on cycle 2 or 3.

Facilities to treat anaphylaxis MUST be present when therapy is administered

Note: Specific Hydration therapy is required for the safe administration of CISplatin (see table below)

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1-4	Dexamethasone	40mg	PO/IV infusion	
1	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% NaCl at a maximum rate of 400mg/hr[1]
1	CISplatin[2]	100mg/m^2	IV infusion	1000ml 0.9% NaCl over 24 hours
2	Cytarabine	2000mg/m^2 **AM**	IV infusion	1000ml 0.9% NaCl over 2 hours
2	Cytarabine	2000mg/m^2 **PM** (12 hours after start of first cytarabine infusion)	IV infusion	1000ml 0.9% NaCl over 2 hours
6 onwards	G-CSF[3]	5mcg/kg (round to nearest whole syringe)	SC	Continued until ANC >1x10^9/L for 2 consecutive days

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

[2]**Pre and post hydration therapy required for CISplatin** See local hospital policy recommendations. Suggested prehydration for CISplatin therapy: 1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes. Administer CISplatin as described above Post hydration: Administer 1000 ml 0.9% NaCl over 60mins Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (4,5).
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.
[3]G-CSF support is required with this regimen **(Refer to local policy or see Suggested support above).**

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.

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to CISplatin, cytarabine, riTUXimab 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, U&Es, LFTs, 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, U&Es, LFTs, LDH prior to each cycle
- Regular glucose monitoring while receiving steroid therapy - urinalysis daily.
  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

Haematological:

Table 2: Dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
<1	and/or	<100	Discuss with Consultant

Renal and Hepatic Impairment:

Table 3: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment
riTUXimab	No dose modification necessary		No dose modification necessary
CISplatin	**CrCl (ml/min)**	**Dose**	No dose modification required
	>60	100%	
	45-59	75%	
	<45	consider carboplatin	
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:

CISplatin: High **(Refer to local policy)**
Cytarabine: Moderate **(Refer to local policy)**
ritUXimab: 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 4: 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 dexamethasone is given at least 30 minutes prior to riTUXimab infusion		

- Hydration prior and post 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)**
- Mouthcare **(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:** DHAP causes severe bone marrow suppression and patients require daily blood monitoring during treatment and at least twice weekly until marrow recovery post therapy.
- **Renal toxicity:** Renal toxicity is common with CISplatin.
- **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 2).
- **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 00542 riTUXimab 375mg/m^2 Combination Therapy – 21 day 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. Monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	08/07/2017 27/06/2017		Prof Elizabeth Vandenberghe Prof Maccon Keane
2	17/10/2018	Updated CISplatin hydration protocol.	Prof Maccon Keane
3	27/06/2022	Clarification of riTUXimab/CD 20+ patients. Amended CISplatin prehydration (KCl), emetogenic potential and adverse effects (hepatitis B reactivation).	Prof Elisabeth Vandenberghe

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.