(R**)-DHAP Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of relapsed Non Hodgkin Lymphoma**</td>
<td>C85</td>
<td>00395a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Treatment of relapsed Hodgkins Lymphoma</td>
<td>C81</td>
<td>00395b</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If a reimbursement status is not defined*, the indication has yet to be assessed through formal HSE reimbursement process.

** RiTUXimab to be included in all CD20 positive patients

TREATMENT:

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 ³CISplatin (see table below)

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Dexamethasone</td>
<td>40mg</td>
<td>PO/IV infusion</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RiTUXimab</td>
<td>375mg/m²</td>
<td>IV infusion ¹</td>
<td>250 to 500ml 0.9% NaCl at a maximum rate of 400mg/hr ³,⁴</td>
</tr>
<tr>
<td>1</td>
<td>³CISplatin</td>
<td>100mg/m²</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 24 hours</td>
</tr>
<tr>
<td>2</td>
<td>Cytarabine</td>
<td>2000mg/m² AM</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 2 hours</td>
</tr>
<tr>
<td>2</td>
<td>Cytarabine</td>
<td>2000mg/m² PM (12 hours after start of first cytarabine infusion)</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 2 hours</td>
</tr>
<tr>
<td>6 onwards</td>
<td>G-CSF</td>
<td>5mcg/kg (round to nearest whole syringe)</td>
<td>SC</td>
<td>Continued until ANC &gt;1x10⁹/L for 2 consecutive days</td>
</tr>
</tbody>
</table>

G-CSF support is required with this regimen (Refer to local policy or see Suggested support above)
**NCCP Chemotherapy Regimen**

- **Pre and post hydration therapy required for CISplatin**
  - See local hospital policy recommendations.
  - Suggested **prehydration** for CISplatin therapy:
    1. Administer 10mmol magnesium sulphate \((\text{MgSO}_4)\) \((+/-\text{KCl 20mmol/L if indicated})\) 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.

- **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**
    - 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.

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

**ELIGIBILITY:**
- Indications as above

**EXCLUSIONS:**
- Hypersensitivity to CISplatin, cytarabine or any of the excipients.
- Moderate/severe renal impairment (creatinine clearance < 60 mL/mi)
- 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 1: Dose modification for haematological toxicity

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 and/or</td>
<td>&lt;100</td>
<td>Discuss with Consultant</td>
</tr>
</tbody>
</table>

Renal and Hepatic Impairment:
Table 2: Dose modifications based on renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISplatin</td>
<td>GFR (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;60</td>
<td>100%</td>
<td>No dose modification required</td>
</tr>
<tr>
<td>45-59</td>
<td>75%</td>
<td>Consider carboplatin</td>
</tr>
<tr>
<td>&lt;45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>GFR (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;60</td>
<td>100%</td>
<td>If bilirubin &gt;34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.</td>
</tr>
<tr>
<td>45-60</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>30-45</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>Avoid</td>
<td></td>
</tr>
</tbody>
</table>

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.

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens
**Table 3: Suggested pre-medications prior to riTUXimab infusion:**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>1g</td>
<td>PO</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>10mg</td>
<td>IV bolus</td>
</tr>
</tbody>
</table>

Ensure dexamethasone is given at least 30 minutes prior to riTUXimab infusion

- Hydration prior and post CIpSplatlin 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 CIpSplatlin.
- **Ootoxicity and sensory neural damage** should be assessed by history prior to each cycle of CIpSplatlin
- **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:** All lymphoma patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.
Please Refer to NCCP Protocol 0020 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. Monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

ATC CODE:
- CISplatin: L01XA01
- Cytarabine: L01BC01

REFERENCES:
NCCP Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>08/07/2017</td>
<td></td>
<td>Prof Elizabeth Vandenberghe</td>
</tr>
<tr>
<td></td>
<td>27/06/2017</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>17/10/2018</td>
<td>Updated Cisplatin hydration protocol.</td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; [http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/](http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/)

2 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.

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