NCCP Chemotherapy Regimen

(R**)- ESHAP 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>00394a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Treatment of relapsed Hodgkin Lymphoma</td>
<td>C81</td>
<td>00394b</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

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

** 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 patient's 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.

<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>1-5</td>
<td>Methylprednisolone</td>
<td>500mg</td>
<td>IV infusion</td>
<td>100ml 0.9% NaCl over 30mins</td>
</tr>
<tr>
<td>1</td>
<td>ritUXimab</td>
<td>375mg/m²</td>
<td>IV infusion¹</td>
<td>250 to 500ml 0.9% NaCl at a maximum rate of 400mg/hr³,4</td>
</tr>
<tr>
<td>1-4</td>
<td>Etoposide</td>
<td>40mg/m²</td>
<td>IV infusion</td>
<td>500ml 0.9% NaCl over 1 hour</td>
</tr>
<tr>
<td>5</td>
<td>Cytarabine</td>
<td>2000mg/m²</td>
<td>IV infusion</td>
<td>1000mls 0.9% NaCl over 2 hours</td>
</tr>
<tr>
<td>1-4</td>
<td>⁸⁵Cisplatin</td>
<td>25mg/m²</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 24 hours</td>
</tr>
<tr>
<td>From day 6 onwards</td>
<td>⁶⁶G-CSF</td>
<td>5mcg/kg</td>
<td>SC (Round to nearest whole syringe)</td>
<td>Continued until ANC &gt;1x10⁹/L for 2 consecutive days</td>
</tr>
</tbody>
</table>

* 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.

** Pre hydration therapy required for Cisplatin
  * See local hospital policy recommendations.
  * Suggested prehydration for Cisplatin therapy:
    1. Administer 10mmol magnesium sulphate (MgSO₄)₁₅₀ | (1+KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.
    * Administer Cisplatin as described above

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

NCCP Regimen: (R**)-ESHAP Therapy
Published: 09/03/2018
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Version number: 1

Tumour Group: Lymphoma
NCCP Regimen Code: 00394
IHS Contributors: Prof Elisabeth Vandeberge

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NCCP Chemotherapy Regimen

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

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Renal and Hepatic Impairment:

Table 1: 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></td>
</tr>
<tr>
<td>45-60</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>consider</td>
<td>carboplatin</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Cr Cl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;50</td>
<td>100%</td>
<td>26-51</td>
</tr>
<tr>
<td>15-50</td>
<td>75%</td>
<td>&gt;51</td>
</tr>
<tr>
<td>&lt;15</td>
<td>50%</td>
<td>Clinical decision</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>GFR (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;60</td>
<td>100%</td>
<td></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.

Table 2: 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 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)
NCCP Chemotherapy Regimen

- 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.
- **Otoxicity 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**: 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. If necessary monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>L01XA01</td>
</tr>
<tr>
<td>Etoposide</td>
<td>L01CB01</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>L01BC01</td>
</tr>
</tbody>
</table>

REFERENCES:


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>Prof Elisabeth Vandeberghe</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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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/profinforonmedonc/cdmp/

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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