R-Gemcitabine (1000mg/m²) Oxaliplatin Therapy - 14 day

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>Relapsed or refractory CD20 positive diffuse large B cell lymphoma in patients ineligible for stem cell transplant.</td>
<td>C83</td>
<td>00506a</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.

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.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>riTUXimab</td>
<td>375mg/m²</td>
<td>IV infusion¹</td>
<td>500ml 0.9% NaCl at a maximum rate of 400mg/hr²</td>
<td>Every 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Observe post infusion¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Gemcitabine</td>
<td>1000mg/m²</td>
<td>IV infusion</td>
<td>250ml 0.9% NaCl over 100mins (i.e. rate of 10mg/m²/min)</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>2</td>
<td>Oxaliplatin</td>
<td>100mg/m²</td>
<td>IV infusion</td>
<td>500ml glucose 5% over 2 hours</td>
<td>Every 14 days</td>
</tr>
</tbody>
</table>

¹The 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.

²Recommended 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.

³Rituximab should be diluted to a final concentration of 1-4mg/ml.

⁴Rapid rate infusion schedule⁴

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
ECOG 0-2

EXCLUSIONS:
- Hypersensitivity to riTUXimab, gemcitabine, oxaliplatin or any of the excipients

PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:
Baseline tests:
- FBC, renal and liver profile
- LDH, Uric acid
- Virology screen-Hepatitis B (HBsAg, HBeAg), Hepatitis C, HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation
- Audiometry and creatinine clearance as clinically indicated

Regular tests:
- FBC, renal, liver profile and LDH prior to each cycle

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:
Prior to commencing a new treatment cycle (i.e day 1), ANC must be >1 x 10^9/L and platelets > 100 x 10^9/L.

### Table 1: Dose modifications for haematological toxicity

<table>
<thead>
<tr>
<th>Day</th>
<th>ANC (x 10^9/L)</th>
<th>Platelet count (x 10^9/L)</th>
<th>Recommended dose of Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥1</td>
<td>≥100</td>
<td>100 %</td>
</tr>
<tr>
<td>1</td>
<td>&lt;1</td>
<td>&lt;100</td>
<td>Delay 1 week, or until resolution. Consider the addition of G-CSF to subsequent cycles.</td>
</tr>
</tbody>
</table>

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Febrile neutropenia
Consider the addition of G-CSF to subsequent cycles
Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>rITUXimab</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Cr Cl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;30</td>
<td>100%</td>
<td>Consider dose reduction. Clinical decision</td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>CrCl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;20</td>
<td>Treat at normal dose and monitor renal function</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>Dose reduce</td>
<td></td>
</tr>
</tbody>
</table>

Management of adverse events:
Table 3: Dose modifications for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity including peripheral neuropathy</td>
<td>Reduce oxaliplatin dose by 25%</td>
</tr>
<tr>
<td>Grade 3 persisting for &gt; 7 days</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
</tr>
<tr>
<td>Laryngo-pharyngeal dysesthesia</td>
<td>Increase infusion time from 2 to 6 hrs</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
Day 1  rITUXimab Minimal
Day 2  Moderate (Refer to local policy).

PREMEDICATIONS:
The following premedication is administered 60 minutes prior to rITUXimab infusion
Paracetamol 1g PO
Chlorphenamine 10mg
Hydrocortisone 100mg IV

OTHER SUPPORTIVE CARE:
Tumour lysis syndrome 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.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

- **Hypersensitivity/Infusion Reactions**: Close monitoring is required throughout the first infusion. (Refer to local policy). rITUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, pruritis, sneezing, cough, fever or faintness.

- **Severe Cytokine Release syndrome**: Usually occurs within 1 to 2 hours of initiating the first infusion. This syndrome may be associated with some features of cytokine release/tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and
NCCP Chemotherapy Regimen

NCCP Regimen: R-Gemcitabine Oxaliplatin Therapy

Published: 13/08/2018
Review: 13/08/2020
Version number: 1

Tumour Group: Lymphoma and Myeloma
NCCP Regimen Code: 00506
ISMO Contributor: Dr Michael McCarthy

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death.
  o Pulmonary interstitial infiltrates or oedema visible on chest x-ray may accompany acute respiratory failure.
  o For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.

• **Progressive multifocal leukoencephalopathy (PML):** Use of riTUXimab may be associated with an increased risk of PML. Patients must be monitored for any new or worsening neurological symptoms. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of rituximab must be permanently discontinued.

• **Infections:** riTUXimab should not be administered to patients with an active, severe infection. Caution should be exercised when considering the use of riTUXimab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.

• **Hepatitis B Reactivation:** This has been reported in patients receiving riTUXimab including fulminant hepatitis with fatal outcome.

• **Vaccines:** Physicians should review the patient’s vaccination status and follow current immunisation guidelines prior to riTUXimab therapy. Vaccination should be completed at least 4 weeks prior to first administration of riTUXimab.
  o The safety of immunisation with live viral vaccines following riTUXimab therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on riTUXimab or whilst peripherally B cell depleted.
  o Patients treated with riTUXimab may receive non-live vaccinations

**Gemcitabine**

• **Pulmonary Toxicity:** Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.

• **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

• **Irreversible renal failure** associated with haemolytic uraemic syndrome may occur rarely with gemcitabine. Use caution with pre-existing renal impairment.

**Oxaliplatin**

• **Platinum Hypersensitivity:** Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.

• **Laryngopharyngeal dysesthesia:** An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1%-2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
NCCP Chemotherapy Regimen

DRUG INTERACTIONS:
- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- Current drug interaction databases should be consulted for more information.

ATC CODE:
- Gemcitabine L01BC05
- riTUXimab L01XC02
- Oxaliplatin L01XA03

REFERENCES:

Version | Date | Amendment | Approved By
--- | --- | --- | ---
1 | 13/08/2018 | | Dr Michael McCarthy

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication 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 aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or “off label” indication has been acknowledged by the hospital’s Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

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/

The rapid infusion is an unlicensed means of administration of rituximab for the indications described above, in Ireland. Patients 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.