NCCP Chemotherapy Protocol

(R*)-CHOP – 14 days

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Protocol Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of Non Hodgkins Lymphoma* (NHL)</td>
<td>C85</td>
<td>00409a</td>
</tr>
</tbody>
</table>

*Rituximab to be included in CD20 positive patients

ELIGIBILITY:
- Indication as above
- Adequate haematological, renal and liver status

EXCLUSIONS:
- Hypersensitivity to DOXOrubicin, cyclophosphamide, riTUXimab, vinCRISTine sulphate or any of the excipients.
- A cumulative life-long dose of 450mg/m² of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Patients in a severely immunocompromised state
- Pregnancy.
- Lactation.

TESTS:
Baseline tests:
- FBC, U&Es, creatinine, LFTs, LDH, blood glucose, Uric Acid, SPEP.
- ECG
- MUGA or ECHO should be considered prior to the administration of DOXOrubicin in high-risk patients
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV

Hepatitis B Reactivation: All lymphoma patients should be tested for both HBsAg and HBcoreAb. 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
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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.

*See Adverse Effects/Regimen Specific Complications

Regular tests:
- FBC, U&Es, LFTs, LDH prior to each cycle.
- Evaluate for peripheral neuropathy prior to each cycle.
- MUGA or ECHO as clinically indicated

Disease monitoring/assessment:
Disease monitoring/assessment should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant

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 consists of R-CHOP administered every 14 days for 6 cycles followed by riTUXimab administered for an additional 2 cycles or until disease progression or unacceptable toxicity develops.

G-CSF support (using standard or pegylated form) is required with all cycles of R-CHOP-14 days.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.
# NCCP Chemotherapy Protocol

## Day 1: R-CHOP Therapy - 14 days

<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>250ml - 500ml 0.9% sodium chloride at a maximum rate of 400mg/hr¹,³</td>
<td>1-8</td>
</tr>
<tr>
<td>1</td>
<td>Cyclophosphamide</td>
<td>750mg/m²</td>
<td>IV infusion²</td>
<td>100 to 250 mL 0.9% NaCl over 20 min to 1 hour</td>
<td>1-6</td>
</tr>
<tr>
<td>1</td>
<td>DOXorubicin⁶</td>
<td>50mg/m²</td>
<td>IV Bolus over 2-15 mins</td>
<td>Into the side arm of a fast running 0.9% NaCl infusion</td>
<td>1-6</td>
</tr>
<tr>
<td>1</td>
<td>VinCRISTine³</td>
<td>1.4mg/m²</td>
<td>IV infusion</td>
<td>50ml minibag 0.9% NaCl over 5-15 minutes</td>
<td>1-6</td>
</tr>
<tr>
<td>1-5</td>
<td>Prednisolone</td>
<td>100mg(++)</td>
<td>PO</td>
<td></td>
<td>1-6</td>
</tr>
</tbody>
</table>

G-CSF support (using standard or pegylated form) is required with all cycles of R-CHOP-14 days.

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 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.

⁵Cyclophosphamide may also be administered as an IV bolus over 5-10mins.

⁶Lifetime cumulative dose of doxorubicin is 450mg/m².

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors below and to the age of the patient.

⁷Vincristine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer. [https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf](https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf)

**Alternative steroid regimens may be used at consultant discretion**
DOSE MODIFICATIONS:
- Any dose modification should be discussed/approved by a Consultant.
- Consider vinCRIStine dose reduction in elderly patients.
- No dose reductions of riTUXimab are recommended.

Haematological:

<table>
<thead>
<tr>
<th>ANC $\times 10^9/L$</th>
<th>Platelets $\times 10^9/L$</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 and/or &lt; 75</td>
<td></td>
<td>Dose modification not generally indicated. Consider treatment delay</td>
</tr>
</tbody>
</table>

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>Cyclophosphamide</td>
<td>GFR (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>≥20</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
</tr>
<tr>
<td>DOXOrubicin</td>
<td>Dose reduce in severe renal impairment</td>
<td>Total Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51-85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If AST 2-3 x normal, give 75% dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If AST &gt;3x ULN, give 50% dose</td>
</tr>
<tr>
<td>VinCRIStine</td>
<td>No dose reduction required</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26-51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;51</td>
</tr>
</tbody>
</table>
**Neurotoxicity:**

Table 1: Dose modification of vinCRIStine based on neurotoxicity (CTCAE v4.0)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Dose of VinCRIStine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hold until recovery then reduce dose by 50%</td>
</tr>
<tr>
<td>Grade 3,4</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Table 2: Dose modification schedule of rITUXimab based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe infusion related reaction (e.g. dyspnkea, bronchospasm, hypotension or hypoxia)</td>
<td>Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x-ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate.</td>
<td></td>
</tr>
<tr>
<td>First occurrence</td>
<td></td>
<td>Consider coverage with steroids for those who are not already receiving steroids.</td>
</tr>
<tr>
<td>Second occurrence</td>
<td>Consider discontinuing treatment</td>
<td></td>
</tr>
<tr>
<td>Mild or moderate infusion-related reaction</td>
<td>Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms</td>
<td></td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

**EMETOGENIC POTENTIAL:** Moderate. (Refer to local policy).

**PREMEDICATIONS:**

Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of rituximab.

Suggested pre-medications:

Chlorpheniramine 10mg IV + paracetamol 1gram PO.

Consider hydrocortisone 100mg-200mg IV 30 minutes prior to therapy in patients not receiving glucocorticoid containing chemotherapy.

**TAKE HOME MEDICATION:**

Prednisolone tablets. See supportive care below.
OTHER SUPPORTIVE CARE:
Tumour lysis syndrome prophylaxis *(Refer to local policy)*
PJP prophylaxis *(Refer to local policy)*
Anti-viral prophylaxis *(Refer to local policy)*
Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRISTine (5)) *(Refer to local policy)*
Prophylactic regimen against vinCRISTine induced constipation is recommended *(Refer to local policy)*.
G-CSF prophylaxis may be required, please discuss with consultant.
Proton pump inhibitor while on prednisolone *(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.

**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.

**Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on RiTUXimab. DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with cardiac dysfunction.

**Neuropathy:** VinCRISTine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRISTine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months. A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRISTine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuation of vinCRISTine and with symptomatic care.

**Extravasation:** DOXOrubicin and vinCRISTine cause pain and possible tissue necrosis if extravasated. *(Refer to local policy).*

**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 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.

**Severe Mucocutaneous Reactions:** These include Steven Johnson syndrome and toxic epidermal necrolysis. Discontinue in patients who develop a severe mucocutaneous reaction. The safety of readministration has not been determined. **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 which 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

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

- Antihypertensives: Additive effect of hypotension during rituximab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-FU, cyclophosphamide or paclitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3AR inhibitors/inducers.

ATC CODE:
RiTUXimab - L01XC02
Cyclophosphamide - L01AA01
DOXOrubicin - L01DB01
VinCRIStine - L01CA02

REIMBURSEMENT CATEGORY:
All of these drugs are funded through local hospital budgets (Jan 2017).

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

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>15/03/2017</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie

1 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.

Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

NCCP Protocol:
R-CHOP Therapy- 14 days
Published: 15/03/2017
Review: 15/03/2019
Version number: 1

Tumour Group: Lymphoma and Myeloma
NCCP Protocol Code: 00409

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In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.