Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE-DOXORUBICIN-PREDNISOLONE-RITUXIMAB-VINCRISTINE
(21)

(RCHOP 21)

There are multiple versions of this protocol in use. Please ensure you have the correct protocol for the relevant diagnosis.

Regimen

- Lymphoma – RCHOP(21)-Cyclophosphamide-Doxorubicin-Prednisolone-Rituximab-Vincristine (21)

Indication

- CD20 positive Non-Hodgkin’s Lymphoma

Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Dysuria, haemorrhagic cystitis (rare), taste disturbances</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Cardiomyopathy, alopecia, urinary discolouration (red),</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Weight gain, gastro-intestinal disturbances, hyperglycaemia,</td>
</tr>
<tr>
<td></td>
<td>CNS disturbances, cushingoid changes, glucose intolerance</td>
</tr>
<tr>
<td>Rituxumab</td>
<td>Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Peripheral neuropathy, constipation, jaw pain</td>
</tr>
</tbody>
</table>

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- Check hepatitis B status before starting rituximab
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems, cardiac risk factors or in the elderly. Discontinue doxorubicin if cardiac failure develops
Dose Modifications

The dose modifications listed are for haematological, liver and renal function and limited drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Dose modifications based on haematological parameters apply to cyclophosphamide and doxorubicin only

<table>
<thead>
<tr>
<th>Neutrophils (x10^9/L)</th>
<th>Dose Modifications (cyclophosphamide and doxorubicin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 on proposed day 1 of cycle</td>
<td>Delay therapy until neutrophils are greater than or equal to 1x10^9/L. Consider G-CSF as secondary prophylaxis. Reconsider treatment options if not recovered after 14 days.</td>
</tr>
<tr>
<td>Grade 4 neutropenia or any febrile neutropenia following any cycle</td>
<td>Give G-CSF with all subsequent cycles</td>
</tr>
<tr>
<td>Grade 4 neutropenia leading to infection despite G-CSF support</td>
<td>Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles</td>
</tr>
<tr>
<td>Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelets (x10^9/L)</th>
<th>Dose Modifications (cyclophosphamide and doxorubicin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 100 on proposed day 1 of cycle</td>
<td>Delay therapy until platelets are greater or equal to 100x10^9/L. Reconsider treatment options if not recovered after 14 days.</td>
</tr>
<tr>
<td>Grade 4 thrombocytopenia following any cycle</td>
<td>Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles</td>
</tr>
<tr>
<td>Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>
Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT (units/L)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Evidence suggest dose modification not necessary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>less than 30</td>
<td>2-3xULN</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>*30-50</td>
<td>More than 3xULN</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>51-85</td>
<td>N/A</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>more than 85</td>
<td>N/A</td>
<td>omit</td>
</tr>
<tr>
<td>Rituximab</td>
<td>N/A</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td>Vincristine</td>
<td>*30-51</td>
<td>60-180</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>more than 51</td>
<td>normal</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>more than 51</td>
<td>more than 180</td>
<td>omit</td>
</tr>
</tbody>
</table>

* Lower limit reflects local practice and may differ from published sources.

Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide**</td>
<td>more than 20</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>less than 10</td>
<td>50%</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>less than 10</td>
<td>Consider dose reduction in severe renal failure</td>
</tr>
<tr>
<td>Rituximab</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td>Vincristine</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
</tbody>
</table>

**Consider mesna in patients with pre-existing bladder disorders. Give an oral dose of 40% of the cyclophosphamide dose (rounded upwards to the nearest 400mg) at 0, 2 and 6 hours after the administration of the cyclophosphamide.
Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops

Rituximab

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab.

Rituximab administration is associated with the onset of cytokine release syndrome. This condition is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. It may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated lactate dehydrogenase (LDH) and can lead to acute respiratory failure and death. This effect on the lungs may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray.

Cytokine release syndrome frequently occurs within one or two hours of initiating the first infusion.

Hypersensitivity reactions, including anaphylaxis, have been reported following the intravenous administration of proteins. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the infusion. Medicinal products for the treatment of allergic reactions should be available for immediate use in the event of hypersensitivity developing during the administration of rituximab.

Use of rituximab maybe associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological, cognitive or psychiatric symptoms that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed the rituximab must be permanently discontinued.

The presence of a viral upper respiratory tract infection at the time of treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment

Vincristine

Reduce the vincristine dose to 1mg if a NCI-CTC grade 2 motor or grade 3 sensory neurological toxicity occurs. For higher toxicity grades or if toxicity increases despite dose reduction stop the vincristine.
Regimen

21 day cycle for 6 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>750mg/m²</td>
<td>1</td>
<td>Intravenous bolus over 10 minutes</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50mg/m²</td>
<td>1</td>
<td>Intravenous bolus over 10 minutes</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 500ml sodium chloride 0.9%</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m²</td>
<td>1</td>
<td>Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>100mg</td>
<td>1, 2, 3, 4, 5</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Consider initial dose reduction in patients over 70 years of age. Doses may be escalated up to full dose on subsequent cycles according to tolerability.

Dose Information

- Cyclophosphamide will be dose banded according to the CSCCN agreed bands
- Doxorubicin will be dose banded according to the CSCCN agreed bands
- The maximum lifetime cumulative dose of doxorubicin is 450mg/m². However prior radiotherapy to mediastinal/pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m²
- Rituximab will be dose rounded to the nearest 100mg (up if half way)
- Vincristine dose will be rounded to the nearest 0.1mg (up if halfway)
- The maximum dose of vincristine is 2mg
Administration Information

Extravasation

- Cyclophosphamide – neutral
- Doxorubicin – vesicant
- Rituximab - neutral
- Vincristine - vesicant

Other

- Prednisolone should be taken in the morning with or after food. Administration of prednisolone begins on the morning of chemotherapy.
- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

Additional Therapy

- Antiemetics
  
  15-30 minutes prior to chemotherapy
  
  - ondansetron 8mg oral or intravenous

  As take home medication
  
  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day for 3 days oral

- Rituximab pre-medication
  
  30 minutes prior to rituximab
  
  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral

On the morning of treatment

- prednisolone 100mg oral to be self administered by the patient on the morning of treatment and for four days after rituximab treatment (this is part of the chemotherapy schedule as well as rituximab pre-medication)
- Rituximab infusion reactions
  - hydrocortisone 100mg intravenous when required for rituximab infusion related reactions
  - salbutamol 2.5mg nebulé when required for rituximab related bronchospasm
  - consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to steroids.

- Allopurinol 300mg once a day oral for the first cycle only

- Consider anti-infective prophylaxis in high risk patients, including:
  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only

- Mouthwashes according to local or national policy on the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

Coding (OPCS 4.6)

- Procurement – X71.4

- Delivery – X72.2

References
REGIMEN SUMMARY

RCHOP(21)-Cyclophosphamide-Doxorubicin-Prednisolone-Rituximab-Vincristine (21)

Cycle 1

1. Warning – Check patient has taken the prednisolone dose*

2. Chlorphenamine 10mg intravenous

3. Paracetamol 1000mg oral

4. Rituximab 375mg/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

5. Ondansetron 8mg oral or intravenous injection

6. Doxorubicin 50mg/m² intravenous bolus over 10 minutes

7. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

8. Cyclophosphamide 750mg/m² intravenous bolus over 10 minutes

9. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

10. Salbutamol 2.5mg nebulie once only when required for the relief of rituximab related bronchospasm

Take Home Medicines

11. Prednisolone 100mg once a day on the morning of the next treatment **

12. Prednisolone 100mg once a day for 4 days oral (starting on day 2)**

13. Metoclopramide 10mg three times a day when required oral

14. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

15. Allopurinol 300mg once a day oral for 21 days
Cycles 2, 3, 4 and 5

1. **Warning** – Check patient has taken the prednisolone dose*
2. Chlorophenamine 10mg intravenous
3. Paracetamol 1000mg oral
4. **Rituximab 375mg/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines**
5. Ondansetron 8mg oral or intravenous injection
6. Doxorubicin 50mg/m² intravenous bolus over 10 minutes
7. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
8. Cyclophosphamide 750mg/m² intravenous bolus over 10 minutes
9. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
10. Salbutamol 2.5mg nebuliser once only when required for the relief of rituximab related bronchospasm

**Take Home Medicines**

11. Prednisolone 100mg once a day on the morning of the next treatment**
12. Prednisolone 100mg once a day for 4 days oral (starting on day 2)**
13. Metoclopramide 10mg three times a day when required oral
14. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

**Cycle 6**

1. **Warning** – Check patient has taken the prednisolone dose*
2. Chlorophenamine 10mg intravenous
3. Paracetamol 1000mg oral
4. **Rituximab 375mg/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines**
5. Ondansetron 8mg oral or intravenous injection
6. Doxorubicin 50mg/m² intravenous bolus over 10 minutes

*Please consult the patient's medical record for specific dosing instructions.**
7. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

8. Cyclophosphamide 750mg/m² intravenous bolus over 10 minutes

9. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

10. Salbutamol 2.5mg nebuloscine once only when required for the relief of rituximab related bronchospasm

**Take Home Medicines**

11. Prednisolone 100mg once a day for 4 days oral (starting on day 2)

12. Metoclopramide 10mg three times a day when required oral

13. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

Administration information

* Please check the patient has taken prednisolone 100mg oral on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone dose please administer prednisolone 100mg oral 30 minutes prior to rituximab administration.

** The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference
**DOCUMENT CONTROL**

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Written By</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>July 2012</td>
<td>“In patients over 70 years of age consider using vincristine 1mg. Where appropriate dose reduction of other agents may be considered at cycle one” changed to “Consider initial dose reduction in patients over 70 years of age.”</td>
<td>Rebecca Wills Pharmacist</td>
<td>Dr Debbie Wright Pharmacist</td>
</tr>
<tr>
<td>1</td>
<td>April 2012</td>
<td>None</td>
<td>Rebecca Wills Pharmacist</td>
<td>Dr Andrew Davies Consultant Medical Oncologist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dr Debbie Wright Pharmacist</td>
<td>Dr Alison Milne Consultant Haematologist</td>
</tr>
</tbody>
</table>

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts:

- Hampshire Hospitals NHS Foundation Trust
- NHS Isle of Wight
- Portsmouth Hospitals NHS Trust
- Salisbury Hospitals NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.