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

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

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

Neutrophils ($x10^9$/L)	**Dose Modifications (cyclophosphamide and doxorubicin)**
Less than 1 on proposed day 1 of cycle	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.
Grade 4 neutropenia or any febrile neutropenia following any cycle	Give G-CSF with all subsequent cycles
Grade 4 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment
Platelets ($x10^9$/L)	**Dose Modifications (cyclophosphamide and doxorubicin)**
Less than 100 on proposed day 1 of cycle	Delay therapy until platelets are greater or equal to $100x10^9$/L Reconsider treatment options if not recovered after 14 days.
Grade 4 thrombocytopenia following any cycle	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment

Hepatic Impairment

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

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

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

Renal Impairment

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

**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

Drug	Dose	Days	Administration
Cyclophosphamide	750mg/m^2	1	Intravenous bolus over 10 minutes
Doxorubicin	50mg/m^2	1	Intravenous bolus over 10 minutes
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%
Vincristine	1.4mg/m^2 (max 2mg)	1	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Prednisolone	100mg	1, 2, 3, 4, 5	Oral

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 nebule 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
1.Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B cell lymphoma. N Engl J Med 2002; 346: 235-242.
2.NICE guidance - TA65 Non-Hodgkin's Lymphoma - rituximab. September 2003
3.NICE guidance – TA137 Lymphoma (follicular non-Hodgkin's) rituximab. February 2008
4.NICE guidance – TA243 Rituximab for the first-line treatment of stage III-IV follicular lymphoma. January 2012
5.Pfreundschuh M, Trümper L, Österborg A et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006; 7: 379-91.

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/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Ondansetron 8mg oral or intravenous injection
6. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes
7. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
8. Cyclophosphamide 750mg/m^2 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 nebule 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. Chlorphenamine 10mg intravenous
3. Paracetamol 1000mg oral
4. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Ondansetron 8mg oral or intravenous injection
6. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes
7. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
8. Cyclophosphamide 750mg/m^2 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 nebule 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. Chlorphenamine 10mg intravenous
3. Paracetamol 1000mg oral
4. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Ondansetron 8mg oral or intravenous injection
6. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes

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

8. Cyclophosphamide 750mg/m^2 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 nebule 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

Version	Date	Amendment	Written By	Approved By
1.2	Jan 2015	Header changed Toxicities removed Hepatic & renal tables updated Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed Disclaimer added Document control reordered	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	July 2012	"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."	Rebecca Wills Pharmacist	Dr Debbie Wright Pharmacist
1	April 2012	None	Rebecca Wills Pharmacist Dr Debbie Wright Pharmacist	Dr Andrew Davies Consultant Medical Oncologist Dr Alison Milne Consultant Haematologist

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.