

Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE-ETOPOSIDE-PREDNISOLONE-RITUXIMAB-VINCRIStINE

(RCEOP)

Regimen

- Lymphoma – RCEOP-Cyclophosphamide-Etoposide-Prednisolone-Rituximab-Vincristine

Indication

- Non Hodgkin's Lymphoma where the use of an anthracycline based regimen is contra-indicated

Toxicity

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

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
- Albumin prior to each cycle
- Check hepatitis B status before starting treatment with rituximab

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and some drug specific toxicities only. 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 etoposide only

Neutrophils ($\times 10^9/L$)	Dose Modifications (cyclophosphamide and etoposide)
1 or greater	100%
0.5 – 0.9	<p>1st Occurrence If the intent is curative and growth factor prophylaxis has <u>not</u> been previously given administer 100% of the dose plus prophylactic growth factors.</p> <p>Alternatively delay until the neutrophils are $1 \times 10^9/L$ or above and then give 75% of the original dose</p> <p>2nd Occurrence Delay until neutrophils are $1 \times 10^9/L$ or above and then give 50% of the original dose plus prophylactic growth factors</p>
less than 0.5 or febrile neutropenia	<p>1st Occurrence Delay until the neutrophils are $1 \times 10^9/L$ or above and then give 75% of the original dose plus prophylactic growth factors</p> <p>2nd Occurrence Delay until the neutrophils are $1 \times 10^9/L$ or above and then give 50% of the original dose plus prophylactic growth factors</p>
Platelets ($\times 10^9/L$)	Dose Modifications (cyclophosphamide and etoposide)
75 or above	100%
50 – 74	<p>1st Occurrence Give 75% of the dose</p> <p>2nd Occurrence Give 50% of the dose</p>
Less than 50 or signs of active haemorrhage	<p>1st Occurrence Delay until the platelets are 75 or above then give 75% of the original dose</p> <p>2nd Occurrence Delay until the platelets are 75 or above then give 50% of the original dose</p>

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 suggests no dose adjustment needed.			
Etoposide	*30-51	Or	60-180	Consider dose reducing to 50%
	more than 51	Or	More than 180	Clinical decision
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

* The 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%
Etoposide	more than 50	100%
	15-50	75%
	Less than 15	50%
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.

Etoposide

Where significant reductions in albumin levels occur consider reducing the dose of etoposide.

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
Etoposide	150mg/m ²	1	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 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
Etoposide	100mg/m ²	2 and 3	Oral
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
- Etoposide (intravenous) will be dose banded according to the CSCCN agreed bands
- Etoposide (oral) is available as 50mg and 100mg capsules. All doses will be rounded to the nearest 50mg (up if halfway)
- Rituximab will be rounded banded to the nearest 100mg (up if halfway)
- 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
- Etoposide – irritant
- Rituximab - neutral
- Vincristine - vesicant

Other

- Etoposide (oral) should be taken an hour before food or on an empty stomach
- 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 oral
- 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 alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.
- 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 – X71.3
- Delivery – X72.1

REGIMEN SUMMARY

RCEOP-Cyclophosphamide-Etoposide-Prednisolone-Rituximab-Vincristine

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. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
7. Etoposide 150mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 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 nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines

11. Etoposide 100mg/m² once a day for 2 days oral (starting on day 2)
12. Prednisolone 100mg once a day on the morning of the next treatment**
13. Prednisolone 100mg once a day for 4 days oral (starting on day 2)**
14. Metoclopramide 10mg three times a day when required oral
15. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment
16. 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/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Ondansetron 8mg oral or intravenous injection
6. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
7. Etoposide 150mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
8. Cyclophosphamide 750mg/m² intravenous bolus over 10 minutes
9. Hydrocortisone 100mg intravenous when required for the relief of rituximab infusion related reactions
10. Salbutamol 2.5mg nebulas when required for the relief of rituximab related bronchospasm

Take Home Medicines

11. Etoposide 100mg/m² once a day for 2 days oral (starting on day 2)
12. Prednisolone 100mg once a day on the morning of the next treatment**
13. Prednisolone 100mg once a day for 4 days oral (starting on day 2)**
14. Metoclopramide 10mg three times a day when required oral
15. 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/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Ondansetron 8mg oral or intravenous injection
6. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
7. Etoposide 150mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

8. Cyclophosphamide 750mg/m² intravenous bolus over 10 minutes
9. Hydrocortisone 100mg intravenous when required for the relief of rituximab infusion related reactions
10. Salbutamol 2.5mg nebulas when required for the relief of rituximab related bronchospasm

Take Home Medicines

11. Etoposide 100mg/m² once a day for 2 days oral (starting on day 2)
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

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.