Chemotherapy Protocol

LYMPHOMA

BLEOMYCIN-CYCLOPHOSPHAMIDE-ETOPOSIDE-MITOXANTRONE-PREDNISOLONE-RITUXIMAB-VINCRISTINE

(RPMitCEBO)

Regimen

- Lymphoma – RPMitCEBO-Bleomycin-Cyclophosphamide-Etoposide-Mitoxantrone-Prednisolone-Rituximab-Vincristine

Indication

- CD20 Positive Non Hodgkin's Lymphoma

Toxicity

Drug	Adverse Effect
Bleomycin	Pulmonary toxicity, rigors, skin pigmentation, nail changes
Cyclophosphamide	Dysuria, haemorrragic cystitis (rare), taste disturbances
Etoposide	Hypotension on rapid infusion, alopecia, hyperbilirubinaemia
Mitoxantrone	Cardiac toxicity, urinary discolouration
Prednisolone	Weight gain, GI 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 (including albumin) and U&Es prior to day one and fifteen
- Regular blood glucose monitoring
- Check hepatitis B status before starting treatment with 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 mitoxantrone if cardiac failure develops.
- Consider performing pulmonary function tests before starting therapy. These should be repeated if respiratory symptoms develop during treatment, particularly a drop in oxygen saturation on exercise. Bleomycin should be stopped until the results of such investigations are known.

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, etoposide and mitoxantrone on **day one and fifteen** only.

Day eight and twenty two of treatment is given irrespective of the haematological counts.

If day one / fifteen is delayed, delay day eight / twenty two accordingly.

Neutrophils ($x10^9$/L)	**Dose Modifications (cyclophosphamide, etoposide, mitoxantrone)**
1 or above	100%
0.5-0.9	1st Occurrence If the intent is curative, the patient has a WHO performance status of 2 or below and has not previously received growth factor prophylaxis administer 100% of the dose with prophylactic growth factors An alternative approach is to delay treatment until the neutrophils are $1x10^9$/L or above and then prescribe 75% of the original dose with prophylactic growth factors 2nd Occurrence Delay until the neutrophils are $1x10^9$/L or above and then reduce the dose by a further 25% of the original dose with prophylactic growth factors
less than 0.5 or febrile neutropenia	1st Occurrence Delay until the neutrophils are $1x10^9$/L or above and then give 75% of the original dose with prophylactic growth factors 2nd Occurrence Delay until the neutrophils are $1x10^9$/L or above and give 50% of the original dose with prophylactic growth factors
Platelets ($x10^9$/L)	**Dose Modifications**
75 or above	100%
50–74	1st Occurrence Give 75% of the original dose 2nd Occurrence Give 50% of the original dose
less than 50 or bleeding	1st Occurrence Delay until the platelets are $75x10^9$/L or above then give 75% of the original dose 2nd Occurrence Delay until the platelets are $75x10^9$/L or above then give 50% of the original dose

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)
Bleomycin				Clinical decision
Cyclophosphamide				Evidence suggests dose reduction not necessary
Etoposide	*30-51	or	60-180	consider dose reduction to 50%
	more than 51	or	more than180	clinical decision
Mitoxantrone	more than 60			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 than180	omit

*Limits reflect local practice and may vary from published sources

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bleomycin	more than 50	100%
	10-50	75%
	less than10	50%
Cyclophosphamide	more than 20	100%
	10-20	75%
	less than10	50%
Etoposide	more than 50	100%
	15-50	75%
	less than15	50%
Mitoxantrone	N/A	No dose adjustment needed
Rituximab	N/A	No dose adjustment needed
Vincristine	N/A	No dose adjustment needed

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.

Bleomycin

The risk of bleomycin induced pneumonitis is greater in those individuals who are older than forty years of age, have a history of smoking, those with underlying lung disease, previous mediastinal radiotherapy, poor renal function or who require growth factors. If pulmonary symptoms develop stop the bleomycin until they can be investigated fully and a diagnosis made.

Etoposide

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

Mitoxantrone

Discontinue mitoxantrone 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 prior to 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

28 day cycle for 3 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	300mg/m^2	1, 15	Intravenous bolus over 10 minutes
Etoposide	150mg/m^2	1, 15	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
Mitoxantrone	7mg/m^2	1, 15	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Rituximab	375mg/m^2	1, 15	Intravenous infusion in 500ml sodium chloride 0.9%
Prednisolone	50mg	1-28 incl	Oral
Prednisolone	50mg alternate days	29-end	Oral
Bleomycin	10 000 International Units /m^2	8, 22	Intravenous bolus over 10 minutes
Vincristine	1.4mg/m^2 (max 2mg)	8, 22	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

Dose Information

- Bleomycin will be dose rounded to the nearest 1000 International Units (up if halfway)
- The maximum cumulative dose of bleomycin is 500 000 International Units in people less than 60 years of age. Refer to SPC for further information in older patients.
- Cyclophosphamide will be dose banded according to the CSCCN agreed bands
- Etoposide will be dose banded according to the CSCCN agreed bands
- Mitoxantrone dose will be rounded to the nearest 1mg (up if halfway)
- The cardiac toxicity of mitoxantrone is more likely to occur at cumulative doses in excess of 160mg/m^2 or 100mg/m^2 after previous anthracycline therapy.
- Rituximab will be dose rounded 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

- Bleomycin - neutral
- Cyclophosphamide – neutral
- Etoposide – irritant
- Mitoxantrone – vesicant
- Rituximab - neutral
- Vincristine - vesicant

Other

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

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy on day 1 and 15

  - ondansetron 8mg oral or intravenous

  As take home medication on day 1 and 15

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

- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral

  On the morning of treatment

  - prednisolone 50mg oral to be self administered by the patient on the morning of 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

- Anti-infective prophylaxis as follows:

    - aciclovir 400mg twice a day oral
    - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only

- Hydrocortisone 100mg intravenous when required for the prevention or treatment of bleomycin related reactions

- 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.

- In order to avoid unnecessary pulmonary toxicity, it is recommended that any GCSF dose scheduled for the day of bleomycin administration is omitted.

Coding (OPCS 4.6)

- Procurement – X71.4

- Delivery – X72.1 day 1 and 15, X72.4 day 8 and 22

References

1.Burton C, Linch D, Hoskin P et al. A phase III trial comparing CHOP to PMitCEBO with or without G-CSF in patients aged sixty plus with aggressive Non-Hodgkins Lymphoma. Br J Cancer 2006; 94 (6): 806-813.
2.Mainwaring PN, Cunningham D, Gregory W et al. Mitoxantrone is superior to doxorubicin in a multi-agent weekly regimen for patients older than 60 with high grade lymphoma: results of a BNLI randomised trial of PAdriaCEBO versus PMitCEBO. Blood 2001; 97 (10): 2991-2997.
3.Pfreundschuh M, Ho A, Wolf M et al. Treatment results of CHOP-21, CHOEP-21, MAC-OPB and PMitCEBO with and without rituximab in young good-prognosis patients with aggressive lymphomas: rituximab as an “equalizer” in the mint (Mabthera international trial group) study. JCO 2005; ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 6529

REGIMEN SUMMARY

RPMitCEBO-Bleomycin-Cyclophosphamide-Etoposide-Mitoxantrone-Prednisolone-Rituximab-Vincristine

Cycle 1 Day 1

1. Warning – Check patient has taken prednisolone dose
   Administration Instructions
   Please check the patient has taken prednisolone 50mg 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 50mg oral 30 minutes prior to rituximab administration.

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

6. Mitoxantrone 7mg/m^2 intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

7. Etoposide 150mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

8. Cyclophosphamide 300mg/m^2 intravenous bolus over 10 minutes

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

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

Take Home Medicines

11. Prednisolone 50mg once a day oral for 28 days

12. Aciclovir 400mg twice a day oral for 28 days

13. Allopurinol 300mg once a day oral for 28 days

14. Co-trimoxazole 960mg once a day oral on Mondays, Wednesdays and Fridays for 28 days

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

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

Cycle 1 Day 8

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

2. Bleomycin 10 000 International Units/m^2 intravenous bolus over 10 minutes

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

Cycle 1 Day 15

1. Warning – Check patient has taken prednisolone dose
   Administration Instructions
   Please check the patient has taken prednisolone 50mg 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 50mg oral 30 minutes prior to rituximab administration.

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

6. Mitoxantrone 7mg/m^2 intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

7. Etoposide 150mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

8. Cyclophosphamide 300mg/m^2 intravenous bolus over 10 minutes

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

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

Take Home Medicines

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

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

Cycle 1 Day 22

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

2. Bleomycin 10 000 International Units/m^2 intravenous bolus over 10 minutes

3. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

Cycles 2 & 3 Day One

1. Warning – Check patient has taken prednisolone dose
   Administration Instructions
   Please check the patient has taken prednisolone 50mg 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 50mg oral 30 minutes prior to rituximab administration.

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

6. Mitoxantrone 7mg/m^2 intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

7. Etoposide 150mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

8. Cyclophosphamide 300mg/m^2 intravenous bolus over 10 minutes

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

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

Take Home Medicines

11. Prednisolone 50mg on alternate days oral for 28 days

12. Aciclovir 400mg twice a day oral for 28 days

13. Co-trimoxazole 960mg once a day oral on Mondays, Wednesdays and Fridays for 28 days

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

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

Cycles 2 & 3 Day 8

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

2. Bleomycin 10 000 International Units /m^2 intravenous bolus over 10 minutes

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

Cycles 2 & 3 Day 15

1. Warning – Check patient has taken prednisolone dose

   Administration Instructions
   Please check the patient has taken prednisolone 50mg 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 50mg oral 30 minutes prior to rituximab administration.

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

6. Mitoxantrone 7mg/m^2 intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

7. Etoposide 150mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

8. Cyclophosphamide 300mg/m^2 intravenous bolus over 10 minutes

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

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

Take Home Medicines

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

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

Cycles 2 & 3 Day 22

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

2. Bleomycin 10 000 International Units /m^2 intravenous bolus over 10 minutes

3. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.4	February 2017	Mitoxantrone changed to vesicant as per EONS guidelines	Donna Kimber Pharmacy Technician	Dr Deborah Wright Pharmacist
1.3	January 2015	Header changed Toxicities removed Hepatic and renal impairment updated Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed Ondansetron TTO clarified Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.2	Sept 2012	"and for four days after rituximab treatment" removed from prednisolone statement in the rituximab premedication section.	Rebecca Wills Pharmacist	Donna Kimber Pharmacy Technician
1.1	Sept 2012	Hydrocortisone administration changed in the summary to the "relief of infusion related reactions"	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	July 2012	None	Rebecca Wills Pharmacist Dr Deborah 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 Hospital 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.