Chemotherapy Protocol

LYMPHOMA

EPIRUBICIN-ETOPOSIDE-IFOSFAMIDE-RITUXIMAB

(RIVE)

Inpatient Regimen

Regimen

Lymphoma – InP-RIVE-Epirubicin-Etoposide-Ifosfamide-Rituximab

Indication

- Non Hodgkin's Lymphoma that is CD20 positive

Toxicity

Drug	Adverse Effect
Epirubicin	Cardiotoxicity, urinary discolouration (red)
Etoposide	Hypotension on rapid infusion, hyperbilirubinaemia
Ifosfamide	Haemorrragic cystitis, encephalopathy, nephrotoxicity
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy

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 of treatment
- EDTA or calculated creatinine clearance prior to each cycle
- 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 epirubicin if cardiac failure develops.
- Urine dip test for protein every four hours the day of and the day after ifosfamide administration
- Fluid balance monitoring every four hours the day of and the day after ifosfamide administration. Urine output should be maintained above 100ml/hour
- Check hepatitis B status before starting treatment with rituximab

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and 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

There are no dose modifications for haematological toxicity. Treatment should be delayed until the minimum criteria, described in the table below, are reached.

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

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

Hepatic Impairment

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

Drug	Bilirubin µmol/L		AST/ALT units	Dose (% of original dose)
Epirubicin	30-50	or	2-4xULN	50%
	51-85	or	more than 4xULN	25%
	more than 85			omit
Etoposide	30-51	or	60-180	Consider dose reducing to 50%
	more than 51	or	more than180	Clinical decision
Ifosfamide	more than 20	or	more than 2.5xULN	Not recommended
	or ALP more than 2.5xULN			
Rituximab	N/A		N/A	No dose adjustments required

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Epirubicin	less than10	Consider dose reduction in severe renal failure
Etoposide	more than 50	100%
	15-50	75%
	less than15	50%
Ifosfamide	more than 60	100%
	40-59	70%
	less than 40	Clinical decision
Rituximab	N/A	N/A

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.

Where appropriate, if dose reductions made at cycle one are well tolerated, dose increases can be considered on subsequent cycles according to tolerability.

Epirubicin

Discontinue epirubicin if cardiac failure develops

Etoposide

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

Ifosfamide

In the case of a NCI-CTC grade 1 neurological toxicity, the dose of ifosfamide may be reduced for the next cycle. If a NCI-CTC grade 2 neurological toxicity appears or neurological toxicity worsens despite dose reduction, the ifosfamide should be stopped.

Risk factors for CNS toxicity include a low albumin, renal impairment, prior administration of cisplatin, poor performance status, CNS tumour, bulky pelvic disease, concomitant psychotropic drugs and younger age. Methylene blue 50mg four times a day intravenous infusion in 100ml sodium chloride 0.9% can be used to prevent or treat ifosfamide induced encephalopathy.

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.

Regimen

3 cycles (1 cycle will be set in Aria)

Drug	Dose	Days	Administration
Epirubicin	50mg/m^2	1	Intravenous injection over 10 minutes
Etoposide	200mg/m^2	1,2,3	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
Mesna	600mg/m^2	1	Intravenous infusion in sodium chloride 0.9% 100ml over 15 minutes
Ifosfamide	1500mg/m^2 twice a day (total daily dose 3000mg/m^2)	1,2,3	Intravenous infusion in sodium chloride 0.9% 1000ml over 12 hours (the ifosfamide and mesna are mixed in the same bag)
Mesna	1500mg/m^2 twice a day (total daily dose 3000mg/m^2)		
Mesna	1800mg/m^2	4	Intravenous infusion in sodium chloride 0.9% 1000ml over 12 hours
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% as per local guidelines

New cycles begin on the day that the neutrophil count recovers to more than 1x10^9/L and the unsupported platelet count is more than 100x10^9/L.

Dose Information

- Epirubicin will be dose banded according to the CSCCN agreed bands
- The maximum lifetime cumulative dose of epirubicin is 900mg/m^2
- Etoposide will be dose banded according to the CSCCN agreed bands
- Ifosfamide will be dose banded according to the CSCCN agreed bands
- Mesna will be dose banded according to the CSCCN agreed bands
- Rituximab dose will be rounded to the nearest 100mg (up if halfway)

Administration Information

Extravasation

- Epirubicin - vesicant
- Etoposide – irritant
- Ifosfamide – neutral
- Mesna - neutral

- Rituximab - neutral

Other

- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines

Additional Therapy

This is an inpatient regimen please ensure all supportive and take home medication are prescribed on the inpatient chart or general prescribing system.

- Rituximab premedication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous (may be omitted if the patient is already taking corticosteroids)
  - paracetamol 1000mg oral

- 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 bolus for rituximab related rigors that fail to respond to corticosteroids.

- Antiemetics

  Starting 15-30 minutes prior to chemotherapy

  - dexamethasone 4mg twice a day for 5 days oral or intravenous
  - metoclopramide 10mg three times a day for 5 days then when required oral or intravenous
  - ondansetron 8mg twice a day for 5 days oral or intravenous

- Growth factor to be continued until the neutrophil count is above $1x10^9$/L. For example:

  - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day from day 7 subcutaneous
  - pegfilgrastim or bioequivalent 6mg once only on day 5 subcutaneous

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

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

- In female patients consider norethisterone 5mg three times a day oral to delay menstruation

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

- Anti-infective prophylaxis as follows:

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

Coding (OPCS 4.6)

- Procurement – X71.5

- Delivery – Not required

References
1.Proctor SJ, Taylor PR, Angus B et al. High dose ifosfamide in combination with etoposide and epirubicin (IVE) in the treatment of relapsed / refractory Hodgkins disease and non-Hodgkins lymphoma: a report on toxicity and efficacy. Eur J Haematol 2001; 64: 28 - 32.
2.McQuaker IG, Haynes AP, Stainer C et al. Stem cell mobilization in resistant or relapsed lymphoma: a superior yield of progenitor cells following a salvage regimen comprising ifosphamide, etoposide and epirubicin compared to intermediate-dose cyclophosphamide. Br J Haematol; 1997; 98:228-233.
3. Bishton MJ, Lush RJ, Byrne JL et al. Ifosfamide, etoposide and epirubicin is an effective combined salvage and peripheral blood stem cell mobilistaion regimen for transplant eligible patients with non-Hodgkins lymphoma and Hodgkin disease. Br J Haematol; 2007: 136: 752-761.

REGIMEN SUMMARY

InP-RIVE-Etoposide-Epirubicin-Ifosfamide-Rituximab

Inpatient Regimen

Other than that listed below, supportive medication for this regimen will not appear on Aria. Please ensure all supportive medication is prescribed on the inpatient chart or general electronic prescribing system.

Day 1

1. Warning – Check supportive medication prescribed
   Administration instructions
   1. Dexamethasone 4mg twice a day, days 1 to 5 oral or intravenous
   2. Metoclopramide 10mg three times a day, days 1 to 5 then as required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
   4. Aciclovir 400mg twice a day oral
   5. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
   6. Growth factor continued until the neutrophil count is above $1x10^9$/L, for example:
      - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
      - lenograstim or bioequivalent 33.6 million units once a day from day 7 subcutaneous
      - pegfilgrastim or bioequivalent 6mg once only on day 5 subcutaneous
   7. Allopurinol 300mg once a day oral (cycle one only)
   8. Consider gastric protection
   9. Consider mouthwashes
   10. Consider norethisterone for menstruating women
   11. Consider pethidine 25-50mg intravenous bolus for rituximab related rigors unresponsive to corticosteroids

2. Chlorphenamine 10mg intravenous injection

3. Hydrocortisone 100mg intravenous injection
   Administration Instructions
   1. Do not administer if corticosteroids have been given as part of the antiemetic or chemotherapy regimen

4. Paracetamol 1000mg oral

5. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% (administer according to local guidelines)

6. Epirubicin 50mg/m^2 intravenous injection over 10 minutes

7. Etoposide 200mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

8. Mesna 600mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

9. Ifosfamide 1500mg/m^2 and mesna 1500mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

10. Ifosfamide 1500mg/m^2 and mesna 1500mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

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

12. Salbutamol 2.5mg nebule when required for rituximab related bronchospasm

Days 2, 3

1. Warning – Check supportive medication prescribed
   Administration instructions
   1. Dexamethasone 4mg twice a day, days 1 to 5 oral or intravenous
   2. Metoclopramide 10mg three times a day, days 1 to 5 then as required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
   4. Aciclovir 400mg twice a day oral
   5. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
   6. Growth factor continued until the neutrophil count is above $1x10^9$/L, for example:
      - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
      - lenograstim or bioequivalent 33.6 million units once a day from day 7 subcutaneous
      - pegfilgrastim or bioequivalent 6mg once only on day 5 subcutaneous
   7. Allopurinol 300mg once a day oral (cycle one only)
   8. Consider gastric protection
   9. Consider mouthwashes
   10. Consider norethisterone for menstruating women
   11. Consider pethidine 25-50mg intravenous bolus for rituximab related rigors unresponsive to corticosteroids

2. Etoposide 200mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

3. Ifosfamide 1500mg/m^2 and mesna 1500mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

4. Ifosfamide 1500mg/m^2 and mesna 1500mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

Day 4

1. Warning – Check supportive medication prescribed
   Administration instructions
   1. Dexamethasone 4mg twice a day, days 1 to 5 oral or intravenous
   2. Metoclopramide 10mg three times a day, days 1 to 5 then as required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
   4. Aciclovir 400mg twice a day oral
   5. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
   6. Growth factor continued until the neutrophil count is above $1x10^9$/L, for example:
      - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
      - lenograstim or bioequivalent 33.6 million units once a day from day 7 subcutaneous
      - pegfilgrastim or bioequivalent 6mg once only on day 5 subcutaneous
   7. Allopurinol 300mg once a day oral (cycle one only)
   8. Consider gastric protection
   9. Consider mouthwashes
   10. Consider norethisterone for menstruating women
   11. Consider pethidine 25-50mg intravenous bolus for rituximab related rigors unresponsive to corticosteroids

2. Mesna 1800mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours
   Administration instructions
   1. To start immediately after the final ifosfamide/mesna infusion bag

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	Mar 2015	Header changed Toxicities removed Hepatic table updated Metoclopramide dose changed to 10mg Growth factor units updated Bolus removed from intravenous bolus throughout text Mucositis recommendation changed Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	Feb 2013	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Alison Milne Consultant Haematologist Dr Andrew Davies Consultant Medical Oncologist

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.