Chemotherapy Protocol

LYMPHOMA

CARBOPLATIN-ETOPOSIDE-IFOSFAMIDE-RITUXIMAB

(RICE)

Ambulatory Regimen

Regimen

- Lymphoma – AmB-RICE-Carboplatin-Etoposide-Ifosfamide-Rituximab

Indication

- Non Hodgkin's Lymphoma that is CD20 positive

Toxicity

Drug	Adverse Effect
Carboplatin	Neuropathy, nephrotoxicity, ototoxicity
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
- Urine diptest 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 $50x10^9$/L

Consider blood transfusion if the patient is symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

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/L**	**Dose (% of original dose)**
Carboplatin	N/A		N/A	No dose adjustment needed
Etoposide	*30-51	or	60-180	50%
	more than 51	or	more than 180	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 adjustment needed

*Limit reflects local practice and may vary from published sources

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Carboplatin	less than 20	omit
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	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.

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% over 30 minutes 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 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 ARA)

New cycles may begin when haematological recovery has taken place. That is on the day that the neutrophil count recovers to more than $1x10^9$/L and the unsupported platelet count is more than $50x10^9$/L.

Please note in the original CORAL study[1] an additional dose of rituximab 375mg/m^2 was given on day -2, cycle 1 only. This does not appear in ARIA but can be added manually at the clinician's discretion.

There are no additional fluids incorporated into this regimen. The patient should be counselled to remain well hydrated and drink between 2-3 litres of fluid per day.

Drug	Dose	Day	Administration
Carboplatin	AUC 5 (max 790mg)	2	Intravenous infusion in 500ml glucose 5% over 60 minutes
Etoposide	100mg/m^2	1, 2, 3	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
Mesna	1000mg/m^2	2	Intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes
Ifosfamide	5000mg/m^2	2	Intravenous infusion in 1000ml sodium chloride 0.9% over 24 hours using a backpack and pump
Mesna	5000mg/m^2	2	
Mesna	1800mg/m^2	3	Oral mesna tablets (rounded upwards to the nearest 400mg) should be given at 0, 2 and 6 hours after the end of the last ifosfamide infusion.
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%

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 $50x10^9$/L.

Dose Information

- Carboplatin will be dose banded in accordance with the national dose bands (10mg/ml)
- The maximum dose of carboplatin is 790mg
- Etoposide will be dose banded in accordance with national dose bands (20mg/ml)
- Ifosfamide will be dose banded in accordance with national dose bands (80mg/ml)
- Mesna will be dose banded in accordance with national dose bands (100 NS)
- Rituximab dose will be rounded to the nearest 100mg (up if halfway)

Administration Information

Extravasation

- Carboplatin - irritant
- Etoposide – irritant
- Ifosfamide – neutral
- Mesna – neutral
- Rituximab – neutral

Other

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

Additional Therapy

This is an ambulatory regimen. Please ensure all supportive and take home medicines are collected / given to the patient. On days two and three ensure the patient has taken this medication before administering any chemotherapy.

- Rituximab premedication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - 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 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 starting oral or intravenous
  - metoclopramide 10mg three times a day when required oral or intravenous
  - ondansetron 8mg twice a day for 5 days oral or intravenous

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

  - filgrastim or bioequivalent 30 million units once a day from day 6 subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day from day 6 subcutaneous
  - pegfilgrastim or bioequivalent 6mg once only on day 4 subcutaneous

  Please check the intention is not to collect stems following the chemotherapy. In this instance the dose of biosimiliar filgrastim will be 10mcg/kg (rounded upwards to the nearest 300microgram or 480microgram). This normally occurs after cycle three.

- 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

References
1.CORAL (Collaborative trial in relapsed aggressive lymphoma) protocol. June 18 2007
2.Kewalramani et al. Rituximab and ICE as second line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B cell lymphoma. Blood 2004; 103:3684-3688.

REGIMEN SUMMARY

AmB-RICE-Carboplatin-Etoposide-Ifosfamide-Rituximab

Day 1

1. Dexamethasone 8mg oral or intravenous
   Administration instructions:
   Administer 30 minutes prior to rituximab

2. Ondansetron 8mg oral or intravenous
   Administration instructions:
   Administer 30 minutes prior to treatment

3. Chlorphenamine 10mg intravenous
   Administration instructions:
   Administer 30 minutes prior to rituximab

4. Hydrocortisone 100mg intravenous injection
   Administration instructions:
   Administer 30 minutes prior to rituximab

5. Paracetamol 1000mg oral
   Administration instructions:
   Administer 30 minutes prior to rituximab

6. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

7. Etoposide 100mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

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

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

Take Home Medicines (day 1 only)

10. Dexamethasone 4mg twice a day for five days starting on day 2 of the cycle oral

11. Ondansetron 8mg twice a day for five days starting on the evening of day one of the cycle oral

12. Metoclopramide 10mg three times a day when required for the relief of nausea oral
    Administration Instructions
    Please supply 28 tablets or the nearest original pack size

13. Mesna 1800mg/m^2 (rounded to the nearest 400mg) oral tablets should be given at 0, 2 and 6 hours after the end of the ifosfamide infusion

14. Aciclovir 400mg twice a day oral for 21 days

15. Co-trimoxazole 960mg once a day on Monday, Wednesday or Friday for 21 days oral

16. 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 6 subcutaneous
    - lenograstim or bioequivalent 33.6 million units once a day from day 6 subcutaneous
    - pegfilgrastim or bioequivalent 6mg once only on day 4 subcutaneous

    Supply 7 days of biosimiliar filgrastim and lenograstim and one biosimiliar pegfilgrastim

    Please check the intention is not to collect stem cells following the chemotherapy. In this instance the dose of biosimiliar filgrastim will be 10mcg/kg (rounded upwards to the nearest 300microgram or 480microgram). This normally occurs after cycle three.

17. Allopurinol 300mg once a day for seven days oral (cycle one only)
    Administration Instructions
    Allopurinol is only required on cycle one.

Day 2

1. Warning – Check supportive medication
   Administration instructions
   Check the patient has taken the prescribed dexamethasone and ondansetron. If they have forgotten administer;
   - dexamethasone 8mg oral or intravenous
   - ondansetron 8mg oral or intravenous

2. Etoposide 100mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

3. Carboplatin AUC 5 (max 790mg) intravenous infusion in 500ml glucose 5% over 60 minutes

4. Mesna 1000mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

5. Ifosfamide 5000mg/m^2 with mesna 5000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 24 hours via a backpack
   Administration Instructions
   The ifosfamide should be mixed in the same bag as the mesna.

Day 3

1. Warning – Check supportive medication
   Check the patient has taken the prescribed dexamethasone and ondansetron. If they have forgotten administer;
   - dexamethasone 8mg oral or intravenous
   - ondansetron 8mg oral or intravenous

2. Etoposide 100mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	February 2023	National dose bands added Maximum dose amended in line with national dose band	Alexandra Pritchard Pharmacist	Tom Hurst Pharmacy Technician
1	July 2017	None	Dr Deborah Wright Pharmacist	Dr Robert Lown 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 that occur as a result of following these guidelines.