**Chemotherapy Protocol**

**LYMPHOMA**

**CARBOPLATIN-ETOPOSIDE-IFOSFAMIDE-RITUXIMAB**

**(RICE)**

**Inpatient Regimen**

## Regimen

- Lymphoma – InP-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.

### *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 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)

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.

| Drug | Dose | Day | Administration |
|---|---|---|---|
| Carboplatin | AUC 5<br>(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 sodium chloride 0.9% 100ml over 15 minutes |
| Ifosfamide | 2500mg/m$^2$ twice a day<br>(total daily dose 5000mg/m$^2$) | 2 | Intravenous infusion in sodium chloride 0.9% 1000ml over 12 hours (the ifosfamide and mesna are mixed in the same bag) |
| Mesna | 2500mg/m$^2$ twice a day<br>(total daily dose 5000mg/m$^2$) | 2 | |
| Mesna | 3000mg/m$^2$ | 3 | Intravenous infusion in sodium chloride 0.9% 1000ml over 8 hours |
| 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 national dose bands (10mg/ml)
- The maximum dose of carboplatin is 800mg in this regimen. This has been set at 790mg in aria to comply with national dose bands.
- 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 administration guidelines

## Additional Therapy

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

- 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 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

InP-RICE-Ifosfamide-Carboplatin-Etoposide-Rituximab

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which must be prescribed on the in-patient chart / general e-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 as required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
   4. Aciclovir 400mg oral 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 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 to the nearest 300microgram or 480microgram). This normally occurs after cycle three.
   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 for rituximab related rigors unresponsive to corticosteroids

2. Chlorphenamine 10mg intravenous

3. Hydrocortisone 100mg intravenous injection

4. Paracetamol 1000mg oral

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

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

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

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

## Day 2

9. 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 as required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
   4. Aciclovir 400mg oral 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 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 to the nearest 300microgram or 480microgram). This normally occurs after cycle three.
   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 for rituximab related rigors unresponsive to corticosteroids

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

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

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

13. Ifosfamide 2500mg/$m^2$ and mesna 2500mg/$m^2$ intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours
    Administration Instructions
    The ifosfamide infusions should be run one after the other. That is, as one infusion ends, the next should begin immediately. The total dose over 24 hours is 5000mg/$m^2$ ifosfamide and 5000mg/$m^2$ mesna in a total volume of 2000ml sodium chloride 0.9%.

14. Ifosfamide 2500mg/$m^2$ and mesna 2500mg/$m^2$ intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours
    Administration Instructions
    The ifosfamide infusions should be run one after the other. That is, as one infusion ends, the next should begin immediately. The total dose over 24 hours is 5000mg/$m^2$ ifosfamide and 5000mg/$m^2$ mesna in a total volume of 2000ml sodium chloride 0.9%.

## Day 3

15. 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 as required oral or intravenous
    3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
    4. Aciclovir 400mg oral 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 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 to the nearest 300microgram or 480microgram). This normally occurs after cycle three.
    7. Allopurinol 300mg once a day oral (cycle one only)
    8. Consider gastric protection
    9. Consider mouthwashes
    10. Consider norethisterone for menstruating women

Consider pethidine 25-50mg intravenous for rituximab related rigors unresponsive to corticosteroids

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

17. Mesna 3000mg/m$^2$ intravenous infusion in 1000ml sodium chloride 0.9% over 8 hours

    Administration instructions

    To start immediately at the end of the last ifosfamide/mesna infusion bag. If required this may be given as oral mesna. A dose of 1800mg/m$^2$ 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.

## DOCUMENT CONTROL

| Version | Date | Amendment | Written By | Approved By |
|---|---|---|---|---|
| 1.3 | May 2023 | National dose banding applied to etoposide, ifosfamide, carboplatin and mesna.<br>Maximum dose of carboplatin amended.<br>Coding removed | Alexandra Pritchard Pharmacist | Tom Hurst Pharmacy Technician |
| 1.2 | July 2017 | Dose change of growth factors noted for harvesting stem cells | Donna Kimber Pharmacy Technician | Dr Deborah Wright Pharmacist |
| 1.1 | Aug 2016 | Header changed<br>Toxicities removed<br>Hepatic impairment guidance updated<br>Administration instructions for hydrocortisone pre med removed<br>Days of dexamethasone administration updated<br>Metoclopramide dose and duration updated<br>“Bolus” removed from “intravenous bolus” for supportive medication throughout text<br>Growth factor units updated<br>Mucositis recommendation changed<br>CSCCN bands removed<br>Administration instructions added to ifosfamide and mesna infusions<br>Mesna infusion changed to 8 hours<br>Disclaimer added | Donna Kimber Pharmacy Technician<br><br>Rebecca Wills Pharmacist | Dr Deborah Wright Pharmacist |
| 1 | August 2012 | None | Rebecca Wills Pharmacist<br><br>Dr Deborah Wright Pharmacist | Dr Alison Milne Consultant Haematologist<br><br>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 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.