Chemotherapy Protocol

LYMPHOMA

CARBOPLATIN-ETOPOSIDE-IFOSFAMIDE

(ICE)

Inpatient Regimen

Regimen

- Lymphoma – InP-ICE-Carboplatin-Etoposide-Ifosfamide

Indication

- Non Hodgkin’s Lymphoma

- Hodgkin’s Lymphoma

Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>Neuropathy, nephrotoxicity, ototoxicity</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Hypotension on rapid infusion, hyperbilirubinaemia</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Haemorrhagic cystitis, encephalopathy, nephrotoxicity</td>
</tr>
</tbody>
</table>

Patients with Hodgkin's Lymphoma carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). Where blood products are required these patients must receive irradiated blood products for life. Local blood transfusion departments must be notified as soon as a diagnosis is made and the patient must be issued with an alert card to carry with them at all times.

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 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
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.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Eligible Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>equal to or more than $1 \times 10^9$/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>equal to or more than $50 \times 10^9$/L</td>
</tr>
</tbody>
</table>

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL. **Irradiated blood products must be used in Hodgkin’s Lymphoma.**

Hepatic Impairment

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin μmol/L</th>
<th>AST/ALT units/L</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>N/A</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td>Etoposide</td>
<td>*30-51</td>
<td>60-180</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>more than 51</td>
<td>more than 180</td>
<td>Clinical decision</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>more than 20</td>
<td>more than 2.5xULN</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>or ALP more than 2.5xULN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Limit reflects local practice and may vary from published sources
Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>less than 20</td>
<td>omit</td>
</tr>
<tr>
<td></td>
<td>more than 50</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>15-50</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>less than 15</td>
<td>50%</td>
</tr>
<tr>
<td>Etoposide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>more than 60</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>40-59</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>Less than 40</td>
<td>Clinical decision</td>
</tr>
</tbody>
</table>

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.
**Regimen**

3 cycles (1 cycle will be set in Aria)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Description</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>AUC 5 (max 790mg)</td>
<td>2</td>
<td>Intravenous infusion in 500ml glucose 5% over 60 minutes</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>1,2,3</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes</td>
</tr>
<tr>
<td>Mesna</td>
<td>1000mg/m²</td>
<td>2</td>
<td>Intravenous infusion in sodium chloride 0.9% 100ml over 15 minutes</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2500mg/m² twice a day</td>
<td>2</td>
<td>Intravenous infusion in sodium chloride 0.9% 1000ml over 12 hours</td>
</tr>
<tr>
<td></td>
<td>(total daily dose 5000mg/m²)</td>
<td></td>
<td>(the ifosfamide and mesna are mixed in the same bag)</td>
</tr>
<tr>
<td>Mesna</td>
<td>2500mg/m² twice a day</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(total daily dose 5000mg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>3000mg/m²</td>
<td>3</td>
<td>Intravenous infusion in sodium chloride 0.9% 1000ml over 8 hours</td>
</tr>
</tbody>
</table>

New cycles begin on the day that the neutrophil count recovers to more than $1 \times 10^9$/L and the unsupported platelet count is more than $50 \times 10^9$/L.

**Dose Information**

- Carboplatin will be dose banded in accordance with national dose bands (10mg/ml)
- The maximum dose for carboplatin in this regimen is 800mg. 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)

**Administration Information**

**Extravasation**

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

- **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 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 1x10⁹/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

- **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.**

- **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

REGIMEN SUMMARY

InP-ICE-Carboplatin-Etoposide-Ifosfamide

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 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 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
   7. Allopurinol 300mg once a day oral (cycle one only)
   8. Consider gastric protection
   9. Consider mouthwashes
   10. Consider norethisterone for menstruating women

2. **Warning** – Check blood transfusion status
   
   **Administration Instructions**
   
   Patients with HODGKIN’S lymphoma carry a lifelong risk of transfusion associated graft versus host disease. Where blood products are required these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life. Ensure transfusion departments are notified and the patient has been issued with an alert card to carry with them at all times.

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

Day 2

4. **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 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
   7. Allopurinol 300mg once a day oral (cycle one only)
   8. Consider gastric protection
   9. Consider mouthwashes
   10. Consider norethisterone for menstruating women

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

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

7. Mesna 1000mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes
8. Ifosfamide 2500mg/m² and mesna 2500mg/m² 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/m² ifosfamide and 5000mg/m² mesna in a total volume of 2000ml sodium chloride 0.9%.

9. Ifosfamide 2500mg/m² and mesna 2500mg/m² 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/m² ifosfamide and 5000mg/m² mesna in a total volume of 2000ml sodium chloride 0.9%.

Day 3

10. 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 then 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 1x10⁹/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  
   7. Allopurinol 300mg once a day oral (cycle one only)  
   8. Consider gastric protection  
   9. Consider mouthwashes  
   10. Consider norethisterone for menstruating women

11. Etoposide 100mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

12. Mesna 3000mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 8 hours  
   Administration instructions  
   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/m² 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

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Written By</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>May 2023</td>
<td>Caboplatin, Ifosfamide, etoposide and mesna updated with national dose banding. Carboplatin maximum dose amended. Coding removed</td>
<td>Alexandra Pritchard</td>
<td>Tom Hurst Pharmacy Technician</td>
</tr>
</tbody>
</table>
| 1.1     | Aug 2016   | Header changed  
Toxicities removed  
Hepatic impairment guidance updated  
Metoclopramide dose and duration updated  
“Bolus” removed from “intravenous bolus” for supportive medication throughout text  
Growth factor units updated  
Mucositis recommendation changed  
OPCS code updated  
“Warning – Check blood transfusion status” added to day 1  
CSCCN removed from dose bands  
Mesna infusion changed from 12 to 8 hours  
Administration instructions added to ifosfamide and mesna infusions  
Disclaimer added                                           | Donna Kimber Pharmacy Technician  | Dr Deborah Wright Pharmacist |
| 1       | August 2012| None                                                                                                                                            | Rebecca Wills Pharmacist | Dr Alison Milne Consultant Haematologist |
|         |            |                                                                                                                                                | Dr Deborah Wright Pharmacist | 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.