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

Drug	Adverse Effect
Carboplatin	Neuropathy, nephrotoxicity, ototoxicity
Etoposide	Hypotension on rapid infusion, hyperbilirubinaemia
Ifosfamide	Haemorrragic cystitis, encephalopathy, nephrotoxicity

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.

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 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.

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			

* 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

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)

Drug	Dose	Days	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 sodium chloride 0.9% 100ml over 15 minutes
Ifosfamide	2500mg/m^2 twice a day (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 (total daily dose 5000mg/m^2)	2	
Mesna	3000mg/m^2	3	Intravenous infusion in sodium chloride 0.9% 1000ml over 8 hours

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 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 $1x10^9$/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

- 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.Moskowitz CH et al. ICE: a highly effective cytoreduction and peripheral blood progenitor cell mobilisation regimen for transplant eligible patients with Non Hodgkin's Lymphoma. Journal of Clinical Oncology 1999; 17: 3776-3785.

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/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%.

9. 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

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 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

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

12. Mesna 3000mg/m^2 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/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
1.2	May 2023	Caboplatin, Ifosfamide, etoposide and mesna updated with national dose banding. Carboplatin maximum dose amended. Coding removed	Alexandra Pritchard Pharmacist	Tom Hurst Pharmacy Technician
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 Rebecca Wills Pharmacist	Dr Deborah Wright Pharmacist
1	August 2012	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 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.