

## Chemotherapy Protocol

### GERM CELL

#### CISPLATIN-IFOSFAMIDE-PACLITAXEL

#### (TIP)

#### Inpatient Regimen

#### Regimen

- Germ Cell – InP-Cisplatin-Ifosfamide-Paclitaxel (TIP)

#### Indication

- Relapsed Metastatic Germ Cell Tumours after failure of first line therapy

#### Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Ifosfamide	Haemorrhagic cystitis, encephalopathy, nephrotoxicity
Paclitaxel	Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

#### Monitoring

#### *Drugs*

- FBC, LFTs and U&Es (magnesium, phosphate and calcium) prior to each cycle
- Serum albumin prior to each cycle
- EDTA or calculated creatinine clearance
- Urine dip test for blood 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
- AFP, HCG on day 1 of the cycle

#### 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.

### Haematological

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

Prior to each cycle the following criteria should be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1 \times 10^9/L$
Platelets	equal to or more than $100 \times 10^9/L$

After each cycle the following table applies to both ifosfamide and paclitaxel.

Neutrophils ( $\times 10^9/L$ )		Platelets ( $\times 10^9/L$ )	Dose (% of original) (ifosfamide and paclitaxel)
1 or above	and	100 or above	100%
1 or above	and	75 - 100	100%
0.5 - 1	and	75 - 100	75%
0.5 - 1	and	50 - 75	50%

This is a potentially curative regimen. All dose reductions and delays should be discussed with the relevant consultant. In general if these levels are not met then treatment should be delayed for three days at a time. Treatment should re-start as soon as these haematological parameters are met. Dose delays rather than dose reductions are recommended.

Cisplatin does not require a dose reduction based on haematological parameters.

### Hepatic Impairment

Drug	Bilirubin $\mu\text{mol/L}$		AST/ALT units/L	Dose
Cisplatin	N/A		N/A	No dose modification necessary
Ifosfamide	greater than ULN	or	greater than 2.5xULN	Not recommended
	or ALP greater than 2.5xULN			
Paclitaxel	less than 25*	and	less than 10xULN	175mg/m <sup>2</sup>
	26-30*			135mg/m <sup>2</sup>
	31-51*			75mg/m <sup>2</sup>
	52-85			50mg/m <sup>2</sup>
	more than 85	or	greater than 10xULN	omit

\*limits reflect local practice and may vary from published sources

## Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin*	more than 60	100%
	If the creatinine clearance is 59ml/min or below please discuss with the relevant consultant*	
Ifosfamide	more than 60	100%
	40-59	70%
	less than 40	clinical decision
Paclitaxel		no dose modification necessary

\*In the original trial<sup>(2)</sup> cisplatin was given at full dose unless the creatinine clearance fell below 40 ml/min, in which case it was discontinued. If the creatinine clearance subsequently recovered to above this level, the cisplatin was initially recommenced at 75% of the original dose.

### 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.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent(s) may then be reduced or discontinued at the discretion of the consultant.

### 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

### 21 day cycle for 4 cycles

Drug	Dose	Days	Administration
Paclitaxel	175mg/m <sup>2</sup>	1	Intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes
Cisplatin	20mg/m <sup>2</sup>	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 120 minutes
Ifosfamide	1000mg/m <sup>2</sup>	1,2,3,4,5	Intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes
Mesna	500mg/m <sup>2</sup>		
Mesna*	500mg/m <sup>2</sup>	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% over 8 hours

\*The last bag of mesna on day 5 of the cycle may be replaced with oral administration at a dose of 400mg/m<sup>2</sup> (rounded upwards to the nearest 400mg capsule) at 0, 2 and 6 hours after the end of the ifosfamide infusion.

## Dose Information

- Aria is set to dose cap all regimens at 2.4m<sup>2</sup>. This regimen must NOT be capped. Please override any doses that are capped.
- Cisplatin 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
- Paclitaxel will be dose banded according to the CSCCN agreed bands

## Administration Information

### *Extravasation*

- Cisplatin - exfoliant
- Ifosfamide - neutral
- Mesna - neutral
- Paclitaxel - vesicant

### *Other*

- Paclitaxel should be administered using a PVC free administration set with a 0.22 micron in-line filter
- Hypersensitivity reactions tend to occur with the first or second infusion of paclitaxel. Paclitaxel infusions should be interrupted for minor symptoms such as flushing or

localised rashes. If these resolve promptly (within 5 minutes) the infusion may be restarted at a lower rate with intensive monitoring. Immediately discontinue the infusion for severe reactions which include profound hypotension, bronchospasm and generalised erythema. In the event of a severe reaction the patient should not be rechallenged with the drug.

### Additional Therapy

This is an inpatient regimen please ensure all supportive and take home medication not on Aria are prescribed on the inpatient chart or general electronic prescribing system.

- Paclitaxel premedication (this will be on Aria)

30 minutes prior to paclitaxel

- chlorphenamine 10mg intravenous
- dexamethasone 20mg intravenous
- ranitidine 50mg intravenous

- Antiemetics

Starting prior to chemotherapy

- aprepitant 125mg once a day on day 1 and 80mg once a day on days 2, 3
- dexamethasone 4mg once a day on days 2, 3, 4, 5, 6, 7 oral
- metoclopramide 10mg three times a day on days 1, 2, 3, 4, 5 then 10mg three times a day when required for nausea oral
- ondansetron 8mg twice a day on days 1, 2, 3, 4, 5, 6, 7 oral

- Cisplatin pre hydration with 500ml sodium chloride 0.9% with 8mmol magnesium sulphate over 30 minutes. The post hydration is incorporated as part of the ifosfamide and mesna administration. Consider furosemide 40mg oral or intravenous for the treatment of fluid overload.

- Growth factor support according to local policy, for example;

- filgrastim or bioequivalent 30 million units once a day for seven days starting on day seven of the cycle subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day for seven days starting on day seven of the cycle subcutaneous
- pegfilgrastim or bioequivalent 6mg once a day for one day on day seven of the cycle

- Ciprofloxacin 500mg twice a day for 7 days starting on day 8 of the cycle oral

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

- Gastric protection with a proton pump inhibitor or a H<sub>2</sub> antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

### Coding (OPCS)

- Procurement – X71.2
- Delivery – Not Required (X72.1 for out-patients)

### References

- 1.Motzer RJ, Sheinfeld J, Mazumdar M. Paclitaxel, ifosfamide and cisplatin second line therapy for patients with relapsed testicular germ cell cancer. J Clin Oncol 2000; 18: 2413-2418.
- 2.Mead GM, Cullen MH, Huddart R et al. A phase II trial of TIP (paclitaxel, ifosfamide, cisplatin) given as second line (post BEP) chemotherapy for patients with metastatic germ cell cancer. Br J Cancer 2005; 93: 178-184.

## REGIMEN SUMMARY

### InP-Cisplatin-Ifosfamide-Paclitaxel (TIP)

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. aprepitant 125mg once a day on day 1 and 80mg once a day on days 2, 3 oral
  2. dexamethasone 4mg once a day on days 2,3,4,5,6,7 oral
  3. metoclopramide 10mg three times a day on days 1,2,3,4,5 then 10mg three times a day when required for the relief of nausea oral
  4. ondansetron 8mg twice a day on days 1,2,3,4,5,6,7 oral
  5. furosemide 40mg oral or intravenous when required for fluid overload
  6. growth factor support according to local policy, for example;
    - filgrastim or bioequivalent 30 million units once a day for seven days starting on day seven of the cycle subcutaneous
    - lenograstim or bioequivalent 33.6 million units once a day for seven days starting on day seven of the cycle subcutaneous
    - pegfilgrastim or bioequivalent 6mg once a day for one day on day seven of the cycle
  7. ciprofloxacin 500mg twice a day for 7 days starting on day 8 oral
2. Chlorphenamine 10mg intravenous
  3. Dexamethasone 20mg intravenous
  4. Ranitidine 50mg in 20ml water for injection intravenous over 2 minutes
  5. Paclitaxel 175mg/m<sup>2</sup> in 500ml sodium chloride 0.9% intravenous infusion over 180 minutes
  6. Sodium chloride 0.9% 500ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes
  7. Cisplatin 20mg/m<sup>2</sup> in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes
  8. Ifosfamide 1000mg/m<sup>2</sup> with mesna 500mg/m<sup>2</sup> in 500ml sodium chloride 0.9% over 60 minutes
  9. Mesna 500mg/m<sup>2</sup> in 1000ml sodium chloride 0.9% over 8 hours

#### Day 2, 3, 4, 5

##### 10. Warning – Check supportive medication prescribed

###### Administration Instructions

1. aprepitant 125mg once a day on day 1 and 80mg once a day on days 2, 3 oral
2. dexamethasone 4mg once a day on days 2,3,4,5,6,7 oral
3. metoclopramide 10mg three times a day on days 1,2,3,4,5 then 10mg three times a day when required for the relief of nausea oral
4. ondansetron 8mg twice a day on days 1,2,3,4,5,6,7 oral
5. furosemide 40mg oral or intravenous when required for fluid overload
6. growth factor support according to local policy, for example;
  - filgrastim or bioequivalent 30 million units once a day for seven days starting on day seven of the cycle subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day for seven days starting on day seven of the cycle subcutaneous
  - pegfilgrastim or bioequivalent 6mg once a day for one day on day seven of the cycle

7. ciprofloxacin 500mg twice a day for 7 days starting on day 8 oral
11. Sodium chloride 0.9% 500ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes
12. Cisplatin 20mg/m<sup>2</sup> in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes
13. Ifosfamide 1000mg/m<sup>2</sup> with mesna 500mg/m<sup>2</sup> in 500ml sodium chloride 0.9% over 60 minutes
14. Mesna 500mg/m<sup>2</sup> in 1000ml sodium chloride 0.9% over 8 hours



## DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	July 2015	Header changed Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed Hepatic impairment table updated, statement added Growth factor units updated Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	June 2013	Mesna dose altered to reflect that used in clinical trial (reference two)	Dr Deborah Wright Pharmacist	Dr Mathew Wheeler Consultant Medical Oncologist
1	Jan 2013	None	Rebecca Wills Pharmacist  Dr Deborah Wright Pharmacist	Dr Joanna Gale Consultant Medical Oncologist  Dr Mathew Wheeler 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.