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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Neuropathy, nephrotoxicity, ototoxicity</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Haemorrhagic cystitis, encephalopathy, nephrotoxicity</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia</td>
</tr>
</tbody>
</table>

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;

<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 $100 \times 10^9$/L</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Neutrophils (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose (% of original) (ifosfamide and paclitaxel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or above and 100 or above</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>1 or above and 75 - 100</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>0.5 - 1 and 75 - 100</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>0.5 - 1 and 50 - 75</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin (μmol/L)</th>
<th>AST/ALT (units/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>N/A</td>
<td>N/A</td>
<td>No dose modification necessary</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>greater than ULN</td>
<td>or greater than 2.5xULN</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>or ALP greater than 2.5xULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>less than 25*</td>
<td>and less than 10xULN</td>
<td>175mg/m^2</td>
</tr>
<tr>
<td></td>
<td>26-30*</td>
<td></td>
<td>135mg/m^2</td>
</tr>
<tr>
<td></td>
<td>31-51*</td>
<td></td>
<td>75mg/m^2</td>
</tr>
<tr>
<td></td>
<td>52-85</td>
<td></td>
<td>50mg/m^2</td>
</tr>
<tr>
<td></td>
<td>more than 85</td>
<td>or greater than 10xULN</td>
<td>omit</td>
</tr>
</tbody>
</table>

*limits reflect 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>Cisplatin*</td>
<td>more than 60</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>If the creatinine clearance is 59ml/min or below please discuss with the relevant consultant*</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>
<tr>
<td>Paclitaxel</td>
<td>no dose modification necessary</td>
<td></td>
</tr>
</tbody>
</table>

*In the original trial\(^2\) 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>175mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20mg/m²</td>
<td>1,2,3,4,5</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 120 minutes</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1000mg/m²</td>
<td>1,2,3,4,5</td>
<td>Intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes</td>
</tr>
<tr>
<td>Mesna</td>
<td>500mg/m²</td>
<td>1,2,3,4,5</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% over 8 hours</td>
</tr>
<tr>
<td>Mesna*</td>
<td>500mg/m²</td>
<td>1,2,3,4,5</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% over 8 hours</td>
</tr>
</tbody>
</table>

*The last bag of mesna on day 5 of the cycle may be replaced with oral administration at a dose of 400mg/m² (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 2.4m². 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 H₂ 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
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/m² 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/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes

8. Ifosfamide 1000mg/m² with mesna 500mg/m² in 500ml sodium chloride 0.9% over 60 minutes

9. Mesna 500mg/m² 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/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes

13. Ifosfamide 1000mg/m² with mesna 500mg/m² in 500ml sodium chloride 0.9% over 60 minutes

14. Mesna 500mg/m² in 1000ml sodium chloride 0.9% over 8 hours
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.