Chemotherapy Protocol

HEAD AND NECK CANCER

CISPLATIN (75)-DOCETAXEL (75)-FLUOROURACIL (4000)

In-Patient Regimen

**Regimen**

- Head and Neck Cancer – InP-Cisplatin(75)-Docetaxel(75)-Fluorouracil (4000)

**Indication**

- Neoadjuvant or advanced squamous cell carcinoma of the head and neck

**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>Docetaxel</td>
<td>Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Diarrhoea, stomatitis</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 prior to each cycle

- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with fluorouracil. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions

**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**

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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Eligible Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>1.5x10⁹/L or greater</td>
</tr>
<tr>
<td>Platelets</td>
<td>100x10⁹/L or greater</td>
</tr>
</tbody>
</table>

Defer treatment for 7 days if the neutrophil count is less than 1.5x10⁹/L and / or the platelet count is less than 100x10⁹/L. If the counts have recovered to these levels at 7 days resume treatment. Consider using a 75% dose reduction. If the counts do not recover delay a further seven days. If they are satisfactory at 14 days treatment can be re-started using a 50% dose reduction.

**Hepatic Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin (μmol/L)</th>
<th>Alk Phos</th>
<th>AST/ALT units</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>N/A</td>
<td>NA</td>
<td>N/A</td>
<td>No dose reduction necessary</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>NA</td>
<td>2.5xULN</td>
<td>1.5xULN</td>
<td>Give 75%</td>
</tr>
<tr>
<td></td>
<td>Greater than ULN</td>
<td>6xULN</td>
<td>3.5xULN or greater</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>less than 85</td>
<td>NA</td>
<td>less than 180</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>more than 85</td>
<td>NA</td>
<td>more than 180</td>
<td>Contra-indicated</td>
</tr>
</tbody>
</table>

**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>45-59</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>less than 45</td>
<td>consider carboplatin</td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td></td>
<td>Consider dose reduction in severe renal impairment only</td>
</tr>
</tbody>
</table>
**Other**

A cycle of chemotherapy should be delayed for up to two weeks to allow for a reduction in the severity of toxic events of NCI-CTC grade 3 or more to a severity of NCI-CTC grade 1 or less (with the exception of alopecia, fatigue, malaise, and nail changes). Delays beyond two weeks required discontinuation of chemotherapy.

**Cisplatin**

Modifications in the dose of cisplatin are necessary for peripheral sensory and motor neurotoxicity, ototoxicity, or nephrotoxicity. Consider stopping treatment for patients with neurotoxicity or ototoxicity of NCI-CTC grade 3 or more.

**Docetaxel**

**Lacrimation**

Excessive lacrimation is related to cumulative docetaxel doses and occurs after a median of 400mg/m². Symptomatic treatment with hyromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 60mg/m².

**Skin**

Delay the docetaxel where a NCI-CTC grade 3 cutaneous toxicity is present on day one of the cycle until it resolves to NCI-CTC grade 1 or below. The subsequent doses of docetaxel should be reduced from 75mg/m² to 60mg/m². If it occurs with a dose of 60mg/m² or if there is no recovery after two weeks, docetaxel treatment should be stopped. Where a NCI-CTC grade 3 cutaneous toxicity occurs between cycles with recovery by day one then reduce the docetaxel dose as described. Docetaxel should be stopped in response to a NCI-CTC grade 4 cutaneous toxicity.

**Fluorouracil**

Modifications in the dose of fluorouracil are necessary for mucositis and diarrhoea.

**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>Cisplatin</td>
<td>75mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/min (minimum time 120 minutes)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride over 60 minutes</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>1000mg/m²</td>
<td>1, 2, 3, 4</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% over 24 hours</td>
</tr>
</tbody>
</table>
Dose Information

- Cisplatin will be dose banded in accordance with the national dose bands (1mg/ml)
- Docetaxel will be dose banded in accordance with the national dose bands (20mg/ml)
- Docetaxel induced fluid retention can lead to weight gain. This is not a reason to alter the doses
- Docetaxel doses of more than 200mg should be diluted in 500ml sodium chloride 0.9% (maximum concentration 0.74mg/ml)
- Fluorouracil will be dose banded in accordance with the national dose bands (50mg/ml)

Administration Information

Extravasation

- Cisplatin – exfoliant
- Docetaxel - exfoliant
- Fluorouracil - inflamitant

Other

- Docetaxel hypersensitivity reactions tend to occur with the first or second infusion. For minor symptoms such as flushing or localised rashes the infusion should not be interrupted. For severe reactions including profound hypotension, bronchospasm and generalised erythema discontinue the infusion immediately.
- The fluorouracil is given as a continuous infusion over 24 hours. A central or PICC line is recommended for treatment to commence and continue.

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy
  - aprepitant 125mg oral day 1
  - aprepitant 80mg oral days 2, 3
  - ondansetron 8mg twice a day oral for 5 days
  - metoclopramide 10mg three times a day when required oral
• Cisplatin pre and post hydration as follows;

Pre

Furosemide 40mg oral or intravenous bolus

1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Post

1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.

• Docetaxel premedication with dexamethasone 8mg oral twice a day the day before, 8mg once a day the day of and the day after docetaxel

• Ciprofloxacin 500mg twice a day for 10 days starting on day 5 of the cycle

• Growth factor according to local formulary choice. For example;
  - filgrastim or bioequivalent 300microgram once a day subcutaneous for seven days starting on day five of the cycle
  - lenograstim or bioequivalent 263microgram once a day subcutaneous for seven days starting on day five of the cycle
  - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two

• Oral loperamide 4mg after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).

• Mouthwashes as per local or national guidelines

• 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

References
REGIMEN SUMMARY

InP-Cisplatin(75)-Docetaxel(75)-Fluorouracil(4000)

Day 1

1. Warning – Check supportive medication prescribed
   Administration instructions
   1. Aprepitant 125mg oral day 1
   2. Aprepitant 80mg oral days 2, 3
   3. Dexamethasone 8mg day 0, 1, 2 or equivalent dose
   4. Metoclopramide 10mg three times a day as required oral or intravenous
   5. Ondansetron 8mg twice a day, days 1, 2, 3, 4, 5 oral or intravenous
   6. Ciprofloxacin 500mg twice a day for 10 days starting on day 5 of the cycle
   7. Growth factors according to local choice
      - filgrastim or bioequivalent 300mcg once a day for 7 days starting on day 5 of the cycle
      - lenograstim or bioequivalent 263mcg once a day for 7 days starting on day 5 of the cycle
      - pegfilgrastim or bioequivalent 6mg once off the day after chemotherapy ends

2. Docetaxel 75mg/m² in 250ml sodium chloride 0.9% over 60 minutes

3. Furosemide 40mg oral or intravenous bolus

4. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

5. Cisplatin 75mg/m² intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 120 minutes)

6. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

7. Fluorouracil 1000mg/m² in 1000ml sodium chloride 0.9% over 24 hours

Day 2, 3, 4

8. Warning – Check supportive medication prescribed
   Administration instructions
   1. Aprepitant 125mg oral day 1
   2. Aprepitant 80mg oral days 2, 3
   3. Dexamethasone 8mg day 0, 1, 2 or equivalent intravenous dose
   4. Metoclopramide 10mg three times a day as required oral or intravenous
   5. Ondansetron 8mg twice a day, days 1, 2, 3, 4, 5 oral or intravenous
   6. Ciprofloxacin 500mg twice a day for 10 days starting on day 5 of the cycle
   7. Growth factors according to local choice
      - filgrastim or bioequivalent 300mcg once a day for 7 days starting on day 5 of the cycle
      - lenograstim or bioequivalent 263mcg once a day for 7 days starting on day 5 of the cycle
      - pegfilgrastim or bioequivalent 6mg once off the day after chemotherapy ends

9. Fluorouracil 1000mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 24 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 NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- Western Sussex Hospitals NHS Trust

All actions have been taken to ensure these protocols are correct. However, it remains the responsibility of the prescriber to ensure the correct drugs and doses are prescribed for patients.