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

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue
Fluorouracil	Diarrhoea, stomatitis

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.

Criteria	Eligible Level
Neutrophils	$1.5x10^9$/L or greater
Platelets	$100x10^9$/L or greater

Defer treatment for 7 days if the neutrophil count is less than $1.5x10^9$/L and / or the platelet count is less than $100x10^9$/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

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

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin	more than 60	100
	45-59	75
	less than 45	consider carboplatin
Docetaxel		No dose adjustment required
Fluorouracil		Consider dose reduction in severe renal impairment only

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 hypromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 60mg/m^2.

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/m^2 to 60mg/m^2. If it occurs with a dose of 60mg/m^2 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

Drug	Dose	Days	Administration
Cisplatin	75mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/min (minimum time 120 minutes)
Docetaxel	75mg/m^2	1	Intravenous infusion in 250ml sodium chloride over 60 minutes
Fluorouracil	1000mg/m^2	1, 2, 3, 4	Intravenous infusion in 1000ml sodium chloride 0.9% over 24 hours

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 H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

References
1. Vermorken JB et al. EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 25: 357 (17): 1695-1704.
2. Lorch JH, Goloubeva O, Haddad RI et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous cell cancer of the head and neck: long term results of the TAX 324 randomised phase III trial. Lancet Oncol 2011; 12 (2): 153-159.

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/m^2 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/m^2 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/m^2 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/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 24 hours

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	Dec 2013	None	Dr Deborah Wright Pharmacist	Dr C Baughan Consultant Clinical 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 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.