Cisplatin/ 5-Fluorouracil for Squamous Cell Carcinoma Head and Neck (HNSCC) – Day unit protocol

Indication:
1) Neoadjuvant: Non-resectable and/or locally advanced Squamous Cell Carcinoma Head and Neck/ Nasopharyngeal HNC
   - Cis80/5FU1000 D1-D4

2) Palliative therapy for Recurrent and/or Metastatic Squamous Cell Carcinoma Head and Neck (Outpatient schedule)
   - Cis100/5FU1000 D1-D4 with concomitant Cetuximab in patients with KPS ≥ 70% where clinically appropriate
   
   Funding and Consultant approval required. See separate protocol for Cetuximab in metastatic/recurrent disease
   - Cis80/5FU1000 D1-D4 in all other patients

Regimen details:
- Cisplatin 80-100mg/m² IV D1
- 5-Fluorouracil (5-FU) 1000mg/m²/24 hours IV D1–D4

Administration:
- Furosemide 40mg orally
- 1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV infusion over 60 minutes
- Cisplatin, in 1 litre Sodium Chloride 0.9% IV over 2 hours
- 1 litre Sodium Chloride 0.9% + 40mmol KCl + 1g MgSO₄ IV infusion over 2 hours
- Then either 500ml Sodium Chloride 0.9% IV infusion over 60 minutes or 500ml drinking water

*Follow guidance protocol for Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens
Any device containing aluminium that may come in contact with Cisplatin must be avoided

5-FU infusion either via peripherally inserted central catheter (PICC) and ambulatory infusion device (this may be attached on the afternoon of Day 1, after the Cisplatin and post-hydration have completed)

OR
Continuous peripheral IV infusion over 4 days (this administration method requires an inpatient admission for the duration of the infusion), given in 4 x 1 litre Sodium Chloride 0.9% (Cisplatin, hydration and any other IV drugs to be administered via a second peripheral cannula). Use this schedule as in-patient ONLY when PICC line can not be done prior to D1 Cycle 1

Frequency:
- Neoadjuvant setting: Every 21 days, for 2 – 3 cycles
- Metastatic disease or Recurrence of SCC: Every 21 days, for 6 cycles (Assess after 3 cycles)
- Stop if obvious clinical or radiological progression and discuss with Consultant

Extravasation:
- Cisplatin and 5FU: Non-vesicants
Anti-emetics: Highly emetogenic. Follow Local Antiemetic Policy

Supportive medication: Loperamide tablet/caps 4mg stat, then 2mg PRN for diarrhoea
Pyridoxine tablets 50mg po tds, if required for palmar-plantar erythema (PPE)
Mouthwashes, when required- refer to local mouthcare guidelines

Regular investigations:
- FBC D1
- LFTs & U&Es D1
- Mg2+ and Ca2+ D1
- EDTA Prior to 1st cycle (if necessary)
- Audiogram Prior to 1st cycle, when clinically indicated
- Disease evaluation After 3 cycles

Comments:

Hydration - Cisplatin
Encourage oral hydration during treatment; for instance, drink a glass of water every hour during treatment, and at least a further 2 litres over the 24 hours following treatment. Weight should be recorded prior to and at the end of Cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and Cisplatin infusion should not be commenced unless this urine output is achieved. For low urine output, consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 kg, or symptoms of fluid overload.

Allergy – Cisplatin
Anaphylactic-like reactions to Cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of Cisplatin administration. Adrenaline, corticosteroids and antihistamines have been effectively employed to alleviate symptoms. No further Cisplatin should be given unless within a “desensitising” protocol.

Electrolyte disturbances – Cisplatin
Disturbances in electrolytes can be a long term manifestation due to the Cisplatin induced renal tubular dysfunction. Check electrolytes- additional supplementation of magnesium, calcium or potassium may be required.

Cardiotoxicity – 5-Fluorouracil
Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris.

Coronary artery spasm is more common in patients receiving continuous infusions of 5FU and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. Standard investigation and treatment of angina may be required. If rechallenge is necessary, this can be performed under Consultant supervision, but should symptoms redevelop, the 5FU should be withdrawn permanently.
DPD deficiency – 5-Fluorouracil
Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced metabolism of fluorouracil, usually manifest as severe toxicity within days of administration. If patients complain of toxicity very soon after administration, it is important to ensure supportive measures are implemented as soon as possible and Consultant consulted before further doses prescribed.

Fertility
Both male and female patients must use contraceptive methods to prevent conception and/or reproduction during and for at least 6 months after chemotherapy. Offer assisted conception counselling (sperm banking for males).

DOSE MODIFICATIONS

Haematological Toxicity

Metastatic or Recurrent disease

WBC < 3.0 x 10⁹/L or Neutrophils < 1.5 x 10⁹/L or Platelets < 100 x 10⁹/L
Delay therapy for 1 week. Repeat FBC – If within normal parameters, proceed with 75% dose of both Cisplatin and 5-FU. If after 1 week the FBC is still not satisfactory, delay therapy for a second week and give subsequent cycles at 50% dose of both Cisplatin and 5-FU.

Neoadjuvant therapy

Neutrophils < 1.0 x 10⁹/L or Platelets < 100 x 10⁹/L
Delay therapy for 3 days and initiate G-CSF support if appropriate. Repeat FBC:
- If recovered: continue with 100% dose in both drugs
- If FBC still low after 3 days, seek Consultant advice

G-CSF support is indicated if Neutrophils < 1.0 x 10⁹/L, to ensure that the next cycle can start on time. Assess patient for any signs of sepsis and counsel patient about appropriate self-care. If in doubt, discuss with doctor.

Renal Impairment:

5FU: Consider dose reduction in severe renal impairment (GFR < 10ml/min) only.

Cisplatin induces nephrotoxicity, which is cumulative. Consider dose reduction following the table below:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
</tr>
<tr>
<td>50 - 60</td>
<td>Give 80%</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Contraindicated. Consider CarboF (AUC 4 – 5)</td>
</tr>
</tbody>
</table>

Reason for Update: Cis 80-5FU & Cis100-5FU amalgamated
Approved by Head and Neck Consultant: T Guerrero Urbano
Version: 1.0
Date: 27.05.2011
Supersedes: All other versions
Checked by (Network Pharmacist): J.Turner
Prepared by: T.Pacheca Palomar
Date: 15.07.2011
Hepatic Impairment: Cisplatin: No dose reduction necessary

Fluorouracil should be used with caution in patients with reduced liver function or jaundice:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST</th>
<th>5FU Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 85</td>
<td>&lt; 180</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&gt; 85 or &gt; 180</td>
<td></td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

PALMAR/PLANTAR ERYTHEMA (PPE)/ MUCOSITIS/ DIARRHOEA – FLUOROURACIL

Patients with any grade PPE should receive Pyridoxine 50mg po tds throughout remainder of treatment
For Grade 2 and above toxicities, PVI 5FU should be discontinued until healing has occurred, and then recommence with dose reduction according to toxicity grading:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Palmar-plantar Erythema</th>
<th>Mucositis</th>
<th>Diarrhoea</th>
<th>5FU Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal skin changes (erythema) without pain</td>
<td>Erythema of the mucosa but normal diet</td>
<td>&lt; 4 stools / day</td>
<td>Give 100%</td>
</tr>
<tr>
<td>2</td>
<td>Skin changes (peeling, blisters, edema) or pain, not interfering with function</td>
<td>Patchy ulcerations, can eat and swallow modified diet</td>
<td>4 – 6 stools / day</td>
<td>Give 75%</td>
</tr>
<tr>
<td>3</td>
<td>Ulcerative dermatitis or skin changes with pain interfering with function</td>
<td>Confluent ulcerations; bleeding with minor trauma. Unable to adequately eat or hydrate orally</td>
<td>≥ 7 stools / day</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>
| 4     | -------------------------- | Tissue necrosis; significant spontaneous bleeding Life-threatening consequences | Life-threatening consequences | Give 25% 
|       |                           |           |            | Discuss with Consultant |

Once dose reduction has been made, all subsequent treatment should remain at reduced dose.

NEUROPATHY/ OTOTOXICITY – CISPLATIN

If patient develops symptoms indicative of Grade 2 or greater Neuropathy (paresthesia interfering with function, but not interfering with activities of daily living) or Ototoxicity (tinnitus not interfering with activities of daily living), seek Consultant advice and consider changing Cisplatin to Carboplatin.

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Approved by Head and Neck Consultant: T Guerrero Urbano
Version: 1.0  Date: 27.05.2011
Supersedes: All other versions  Checked by (Network Pharmacist): J.Turner
Prepared by: T.Pacheca Palomar  Date: 15.07.2011
<table>
<thead>
<tr>
<th>Grade</th>
<th>Neuropathy-sensory</th>
<th>Ototoxicity</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paresthesia (including tingling) but not interfering with function</td>
<td>--------</td>
<td>Give 100%</td>
</tr>
<tr>
<td>2</td>
<td>Paresthesia interfering with function, but not interfering with activities of daily living</td>
<td>Tinnitus not interfering with activities of daily living</td>
<td>Give 80%</td>
</tr>
<tr>
<td>3</td>
<td>Paresthesia interfering with activities of daily living</td>
<td>Tinnitus interfering with activities of daily living</td>
<td>Consider changing Cisplatin to Carboplatin Discuss with Consultant</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Disabling</td>
<td>Change Cisplatin to Carboplatin Discuss with Consultant</td>
</tr>
</tbody>
</table>

**Toxicities:** Myelosuppression; fatigue; nausea; vomiting; constipation; diarrhoea; mucositis; stomatitis; nephrotoxicity; neuropathy / ototoxicity; cardiotoxicity; taste disturbance; electrolyte disturbances; allergic reactions; palmar-plantar erythema (PPE); ovarian failure; infertility; alopecia

**Drug interactions:**

**Cisplatin**
- Allopurinol, colchicine, probenecid, sulfinpyrazone: increase in serum uric acid concentration
- Cefalosporins, aminoglycosides, amphotericin B: increase nephrotoxic and ototoxic effects of Cisplatin in these organs
- Ciclosporine: excessive immunosuppression, with risk of lymphoproliferation
- Cyclazine, phenothiazines: may mask ototoxicity symptoms
- Furosemide (high doses), hydralazine, diazoxide and propranolol: intensify nephrotoxicity
- Oral anticoagulants: require an increased frequency of the INR monitoring
- Penicillamine: may diminish the effectiveness of Cisplatin
- Phenytoin: reduced epilepsy control

**Fluorouracil**
- Allopurinol: avoid concomitant use
- Clozapine: increased risk of agranulocytosis, avoid concomitant use
- Coumarins: enhanced anticoagulant effect
- Digoxin tablets: reduced absorption (resolved by giving the digoxin in liquid)
- Leucovorin: increased cytotoxic and toxic effects of Fluorouracil
- Metronidazole; Cimetidine: inhibit metabolism of fluorouracil (increased toxicity)
- Phenytoin: reduced absorption of the antiepileptic
- Sorivudine: marked and rapidly fatal fluorouracil toxicity
References:

[www.medicines.org.uk](http://www.medicines.org.uk)


Al-Sarraf M et al. JCO (1998); Vol 16 (4):1310 – 1317


Domenge C et al. Br J Cancer (2000); 83: 1594 -1598


Langendijk JA et al. JCO (2004), Vol 22 (22): 4604 - 4612


Pignon JP et al. Radiotherapy and Oncology (2009); 92: 4 – 14

Psyrri A et al. JCO (2004); 22: 3061 – 3069

Vermocken et al. NEJM (2008); 359:1116-27

Zorat PL et al. J Natl Cancer Inst (2004); 96: 1714 -1717

COIN guidelines, October 2000


UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003

UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003

Stockley’s Drug Interactions. Interactions search: Cisplatin&Fluorouracil. July 09

CTCAE v3.0. August 2006