Cisplatin / 5-Fluorouracil plus Radiotherapy for Oesophageal or Gastro-oesophageal Cancer

Indication: Primary therapy for patients with localized carcinoma of the Oesophagus selected for non surgical treatment

Regimen details:

Chemotherapy:  
- Cisplatin 75mg/m² IV D1 of Weeks 1, 5, 8 & 11  
- 5-Fluorouracil (5-FU) 1000mg/m²/24 hours IV D1–D4 of Weeks 1, 5, 8 & 11

Radiotherapy (RT): 50 Gy over 25 fractions (2 Gy/#) on Mondays to Fridays, with concurrent chemotherapy from week 1 to week 5

Cisplatin must have been running for at least one hour before RT administered on D1, but it is not necessary for 5-FU to have been initiated; 5-FU must be initiated on the afternoon of Day 1 in readiness for RT doses during the remainder of the week

Administration:
- Furosemide 40mg orally
- 1 litre Sodium Chloride 0.9% + 20mmol KCl + 1g Mg SO₄ IV infusion over 60 minutes
- Cisplatin in 1000ml Sodium Chloride 0.9% over 2 hours
- 1 litre Sodium Chloride 0.9% + 40mmol KCl + 1g Mg SO₄ 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 central venous catheter 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 96 hours (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)

Frequency:  
- Cycles 1 & 2: Chemo-radiotherapy (weeks 1 and 5)  
- Cycles 3 & 4: Chemotherapy only (weeks 8 and 11)  
- Usually 4 cycles. See also Appendix 1, Treatment summary on page 6

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
- LFTs & U&Es
- Mg²⁺ and Ca²⁺
- EDTA (Prior to 1st cycle, if necessary)
- Toxicity assessment (during RT) - Weekly
- Audiogram (Prior to 1st cycle, when clinically indicated)

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

DOSE MODIFICATIONS

Haematological Toxicity

As this is potentially curative, chemotherapy should not be delayed. If patient presents with low blood counts, do not defer but continue with doses according to the advice below, followed by G-CSF rescue (starting on Day 5 of the cycle) if appropriate:

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>or</th>
<th>Platelets</th>
<th>Cisplatin and 5-FU Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 – 1.5 x 10^9/L</td>
<td>50 – 74 x 10^9/L</td>
<td>Give 75% Cisplatin dose and full dose 5-FU</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 x 10^9/L</td>
<td>&lt; 50 x 10^9/L</td>
<td>Review dose on each cycle, according to FBC</td>
<td></td>
</tr>
</tbody>
</table>

Renal Impairment: GFR should be calculated using the Cockcroft & Gault equation in all patients; if the calculated GFR < 60 or > 120ml/min, measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if 25% from baseline value, re-calculate GFR using the Cockcroft & Gault equation

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

Cisplatin induces nephrotoxicity, which is cumulative. It is therefore contraindicated in patients with renal impairment. 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>51– 60</td>
<td>Give 75%</td>
</tr>
<tr>
<td>40 – 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Contraindicated Consider Carboplatin-Discuss with Consultant</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

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>
<tr>
<td>4</td>
<td>------------------------</td>
<td>Tissue necrosis; significant spontaneous bleeding Life-threatening consequences</td>
<td>Life-threatening consequences</td>
<td>Give 25% Discuss with Consultant</td>
</tr>
</tbody>
</table>

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 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.

Toxicities: Myelosuppression; fatigue; nausea; vomiting; diarrhoea; mucositis; stomatitis; nephrotoxicity; neuropathy/ ototoxicity; cardiotoxicity; fever; palmar-plantar erythema (PPE); ovarian failure; infertility; anaphylactic-like reactions; alopecia

Drug interactions: 5-Fluorouracil is a known radiation-sensitizer. Patients should be carefully monitored for gastrointestinal toxicity when they are receiving concurrent 5-FU-Radiation therapy.
Cisplatin
- Allopurinol, colchicine, probenecid, sulfinpyrazone: increase in serum uric acid concentration
- Cephalosporins, aminoglycosides, amphotericin B: increase nephrotoxic and ototoxic effects of Cisplatin in these organs
- Ciclosporine: excessive immunosuppression, with risk of lymphoproliferation
- Cyclizine, 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
Minsky BD et al. JCO (2002); Vol 20 (5):1167-1174
CCO Formulary- FU-CISP*HI. Revised October 2004
SWSHCN- Approved Network Upper GI Regimen. April 2007
COIN guidelines, October 2000
Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens. Mar’06
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
Stockley’s Drug Interactions. Interactions search: Cisplatin&Fluorouracil. July 08
CTCAE v3.0. August 2006
### Appendix 1 Treatment summary

**Weeks 1 and 5:** Chemo-radiotherapy (RT given over 5 following weeks)
**Weeks 8 and 11:** Chemotherapy only

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Cisplatin</th>
<th>75mg/m²</th>
<th>IV</th>
<th>D1 of Weeks 1, 5, 8 &amp; 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-FU</td>
<td>1000mg/m²/24 hours</td>
<td>IV</td>
<td>D1-D4 of Weeks 1, 5, 8 &amp; 11</td>
</tr>
</tbody>
</table>

**Radiotherapy (RT):**  50 Gy over 25 fractions (2 Gy/#) on Mondays to Fridays, with concurrent chemotherapy from week 1 to week 5

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>1 - 5</td>
<td>8 - 12</td>
<td>15 - 19</td>
<td>22 - 26</td>
<td>29 - 33</td>
<td>50 - 54</td>
<td>71 - 75</td>
</tr>
<tr>
<td>RT</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☒ ☒ ☒ ☒ ☒</td>
<td>☒ ☒ ☒ ☒ ☒</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>5-FU</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
</tbody>
</table>

- ☐: Give RT on that day
- ↑: Give chemotherapy on that day
- •: Do NOT give RT on that day