ECF: Epirubicin / Cisplatin / PVI 5-Fluorouracil for Locally Advanced and Metastatic Non Squamous Cell Carcinoma Head and Neck

Indication:
- Palliative therapy for Locally Advanced and Metastatic:
  - Adenocarcinoma Head and Neck
  - Salivary gland carcinoma (adenoid cystic carcinoma)
  - Thyroid carcinoma (medullary, poorly differentiated papillary and follicular)

Regimen details:
- Epirubicin: 50mg/m² IV D1
- Cisplatin: 60mg/m² IV D1
- 5-Fluorouracil (5-FU): 200mg/m²/24hrs IV continuous infusion D1 – D21

Administration:
- Furosemide 40mg orally
- 1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV infusion over 60 minutes
  - Epirubicin: IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion
  - Cisplatin: in 1 litre Sodium Chloride 0.9% IV 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, 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)
The Protracted Venous Infused (PVI) 5-FU is continued for a total of 18 weeks if given for 6 cycles

Frequency:
- Every 21 days, for 6 cycles

Extravasation:
- Epirubicin: Vesicant
- 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)
- If warfarin is used as thromboprophylaxis, it should be dosed to a target INR of 1.5

Regular investigations:
- FBC D1
- LFTs & U&Es D1
- Mg²⁺ and Ca²⁺ D1
- EDTA Prior to 1st cycle (if necessary)
- MUGA scan See Comments (if necessary)
- CT scan or MRI Head After 3 cycles
Comments:  
Cardiotoxicity – Epirubicin  
Maximum cumulative dose Epirubicin = 950mg/m²  
A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum.

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 5-FU and is usually reversible on discontinuing the infusion. Should a patient receiving 5-FU present with chest pains, stop the 5-FU. 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 5-FU 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

WBC < 3.0 x 10⁹/L or Neutrophils < 1.5 x 10⁹/L or Platelets < 100 x 10⁹/L

Delay all drugs for 1 week or until the myelosuppression is resolved.

After 1 week, repeat FBC and, if normal, resume treatment at full doses

- If there is a 2-week delay, give all drugs at 75% doses
- If > 2 week delay, consider discontinuing therapy

Discuss with Consultant

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

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

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 ECaRboF. Discuss with Consultant</td>
</tr>
</tbody>
</table>

Hepatic Impairment

Cisplatin: No dose reduction necessary

5-FU 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>5-FU 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>

Epirubicin is mainly metabolised in the liver. Consider dose reduction as follows:
**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 5-FU 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>5-FU 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>Tissue necrosis; significant spontaneous bleeding</td>
<td>Life-threatening consequences</td>
<td>Life-threatening consequences</td>
<td>Give 25%</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; nausea; vomiting; diarrhoea; mucositis; stomatitis; fatigue; nephrotoxicity; neuropathy/ ototoxicity; cardiomyopathy; coronary artery spasm; fever; palmar-plantar erythema (PPE); urine discoloration; ovarian failure; infertility; electrolyte disturbances; alopecia

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**Bilirubin (µmol/L) vs. Epirubicin Dose**

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Epirubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 52</td>
<td>Give 50%</td>
</tr>
<tr>
<td>51 – 85</td>
<td>Give 25%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>Omit</td>
</tr>
</tbody>
</table>
Drug interactions:

Epirubicin
- Cimetidine and Ciclosporin: can increase epirubicin serum levels
- Clozapine: increased risk of agranulocytosis, avoid concomitant use
- Digoxin tablets: reduced absorption (resolved by giving the digoxin in liquid)
- Phenytoin: reduced absorption of the antiepileptic
- Verapamil: possibly increases epirubicin bone marrow depressant effects

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

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