Cisplatin / 5-Fluorouracil for Neoadjuvant Oesophageal Cancer

Indication: Neoadjuvant therapy for resectable Oesophageal Cancer

Regimen details:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>80mg/m²</td>
<td>IV</td>
<td>D1</td>
</tr>
<tr>
<td>5-Fluorouracil (5-FU)</td>
<td>1000mg/m²/24 hours</td>
<td>IV</td>
<td>D1–D4</td>
</tr>
</tbody>
</table>

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: Every 21 days, 2 cycles only (prior to surgery)

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:

<table>
<thead>
<tr>
<th>Test</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>D1</td>
</tr>
<tr>
<td>LFTs &amp; U&amp;Es</td>
<td>D1</td>
</tr>
<tr>
<td>Mg²⁺ and Ca²⁺</td>
<td>D1</td>
</tr>
<tr>
<td>EDTA</td>
<td>Prior to 1st cycle (if necessary)</td>
</tr>
<tr>
<td>Audiogram</td>
<td>Prior to 1st cycle, when clinically indicated</td>
</tr>
</tbody>
</table>

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

Renal impairment – Neo-adjuvant setting
In Neo-adjuvant setting, it is imperative that patients going to surgery do not have significant reduction in renal function. If GFR < 60ml/min, discuss with Consultant before proceeding. For patients in Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. However, if borderline, discuss with Consultant before proceeding. Cisplatin dose should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine

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

WBC < 3.0 x 10⁹/L
or
Neutrophils < 1.0 x 10⁹/L
or
Platelets < 100 x 10⁹/L

Delay by 1 week. Repeat FBC and, if within normal limits, continue with 75% dose of both Cisplatin and 5-FU. If after 1 week, the result is not satisfactory, delay treatment for a second week, then continue with 50% doses of both Cisplatin and 5-FU.

Renal Impairment:

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

Cisplatin induces nephrotoxicity, which is cumulative. If GFR < 60ml/min, discuss with Consultant before proceeding. It is imperative that patients going to surgery do not have significant reduction in renal function. 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</td>
</tr>
<tr>
<td></td>
<td>Consider CarboF (AUC 5)*</td>
</tr>
<tr>
<td></td>
<td>Discuss with Consultant</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Carboplatin contraindicated</td>
</tr>
</tbody>
</table>

* Carboplatin dose should be calculated using the Calvert Formula:
Dose = Target AUC x (25 + GFR)

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>Tissue necrosis; significant spontaneous bleeding</td>
<td>Life-threatening consequences</td>
<td></td>
<td>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; alopecia; diarrhoea; mucositis; stomatitis; nausea; vomiting; nephrotoxicity; neuropathy/ ototoxicity; cardiac disorders; coronary artery spasm; fatigue; fever; palmar-plantar erythema (PPE); ovarian failure; infertility; anaphylactic-like reactions; electrolyte disturbances; excessive lacrimation

Drug interactions:

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:

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