CISPLATIN & FLUOROURACIL

Indication: Carcinoma of the Anus, palliative intent in advanced disease

Drugs/ Dosage: Cisplatin 80mg/m² IV D1
5-Fluorouracil 1000mg/m² IV D1-D4

Administration: 1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV over 60 minutes
Mannitol 20% 100ml IV over 30 minutes
Cisplatin in 1000ml 0.9% Sodium Chloride over 2 hrs
1 litre 0.9% Sodium Chloride + 40 mmol KCl + 1g MgSO₄ IV over 2 hours
Then either 500ml Sodium Chloride 0.9% IV over 60 minutes or 500ml drinking water
*Follow guidance protocol for Hydration schedules & fluid balance monitoring for outpatient cisplatin regimens
5FU infusion either via central venous catheter and ambulatory infusion device or continuous peripheral IV infusion **over 96 hours (4 days),** given in 4 x 1 litre N/Saline.

Frequency: Cycles 1 and 2 concomitant with radiotherapy (weeks 1 and 5), 4 weekly cycle
Cycles 3 and 4 without radiotherapy, 3 weekly cycle
Usual total 2-4 cycles

Main Toxicities: myelosuppression; alopecia (mild/ moderate), mucositis; diarrhoea, neurotoxicity (see Comments); hand-foot syndrome (PPE); allergic reactions (see Comments); cardiotoxicity (uncommon); ovarian failure/infertility, nephrotoxicity, ototoxicity, line thrombus

Anti-emetics: D1- Highly emetogenic, D2-4 mildly emetogenic

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

Extravasation: Non-vesicant

Regular investigations: FBC D1
U&Es D1
Mg²⁺,Ca D1
LFTs D1
(EDTA Prior to 1st cycle- see comments below)
Audiogram Prior to 1st cycle when clinically indicated

Comments: 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.

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.

*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.

**Toxicities and Dose Modifications**

**Haematological Toxicity on D1**

Neutrophils ≥ 1.0 x 10⁹/l and Platelets ≥ 100 x 10⁹/l  
Proceed with treatment

Neutrophils < 1.0 x 10⁹/l or Platelets < 100 x 10⁹/l  
Delay treatment for 1 week. Repeat FBC and, if recovered, no dose adjustment required.

- If patient suffers an episode of Grade 3 febrile neutropenia, continue after recovery with cisplatin 50mg/m² and 5FU at 75% of original dose.
- For Grade 4 neutropenic sepsis or 2nd occurrence of grade 3, discuss with Consultant.

**Renal Impairment**

Before every course, calculate CrCl using Cockcroft and Gault. If borderline, an EDTA should be requested.

<table>
<thead>
<tr>
<th>CrCl (C&amp;G)(ml/min)</th>
<th>Cisplatin Dose</th>
<th>Fluorouracil Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
<td>100%</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>Carboplatin suggested, or Cisplatin 50%</td>
<td>100%</td>
</tr>
<tr>
<td>(45-59)</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Carboplatin contra-indicated</td>
<td>80%</td>
</tr>
</tbody>
</table>

Cisplatin-induced nephrotoxicity is dose-related and cumulative. It manifests early by elevations in blood urea, creatinine, and wasting of potassium and magnesium. Renal function, fluid and electrolyte balance must return to normal prior to subsequent doses. Renal toxicity may be irreversible and is more prolonged and severe with repeated courses. Avoid concomitant use of other nephotoxic drugs (see ‘Drug interactions’).

**Hepatic Impairment**

Bilirubin > 3 x ULN (unless secondary to biliary obstruction) or ALT/AST > 2.5 ULN  
Give 50% of 5FU until liver function recovers, increase dose if no further toxicity
Non-Haematological Toxicities

*Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.*

Toxicity due to 5FU administration may be managed symptomatically and/or modification of the dose. Once the dose has been reduced, it should not be increased at a later time. Doses of 5FU omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

**Fluorouracil non-haematological toxicity dosing table:**

<table>
<thead>
<tr>
<th>Diarrhoea, abdo pain, N&amp;V, Stomatitis</th>
<th>Immediate action</th>
<th>Dose next cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>maintain dose</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2 1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2 2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>Grade 2 3rd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>Grade 2 4th appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 3 1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>Grade 3 2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>Grade 3 3rd appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 4 1st appearance</td>
<td>Discontinue or at consultants discretion</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Palmar-Plantar Erythema</th>
<th>Immediate action</th>
<th>Dose next cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>maintain dose</td>
<td>100%</td>
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<td>Grade 3 2nd appearance</td>
<td>Discontinue or at consultants discretion</td>
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</tr>
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In Grade 3 or 4 stomatitis or diarrhoea, reduce Cisplatin to 75% dose.
Other Toxicities

Cardiotoxicity

Coronary artery spasm is a recognised complication of fluoropyrimidines although the evidence base regarding aetiology, management & prognosis is not particularly strong. The incidence is estimated to be between 2% and 18%. Coronary artery spasm is usually reversible on discontinuing the treatment. Should a patient receiving 5FU present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, 5FU should be withdrawn permanently. Refer to Consultant to discuss.

Neurotoxicity

Caution must be exercised in patients with central or peripheral nervous system disease e.g. cerebral metastasis or neuropathy
Grade 2 neurotoxicity requires a 50% dose reduction of cisplatin. For Grade 3 or 4 neurotoxicity, treatment should be discontinued.

Drug Interactions:

Coumarin anticoagulants-monitor INR
Phenytoin, carbamazepine- altered plasma levels
Nephrotoxic drugs, Ototoxic drugs (Cisplatin)
Metronidazole- increased plasma levels and toxicity
Folinic acid- increased toxicity
Allopurinol- reduced efficacy
Antacids- absorption interference

References:
Summerhayes et al. Practical chemotherapy. 2003
Royal Surrey County Hospital chemotherapy protocols
www.medicines.org.uk
Micromedex review, Fluorouracil. Sept 2007
BCCA Protocol summary. GIFUC. Revised Oct 2007
CCO formulary; FU-CISP*LO & *HI. Revised Oct 2004
MRC OE05 Trial.