Cisplatin / 5-Fluorouracil plus Radiotherapy for Vulval Cancer

Indication: Primary Neoadjuvant therapy with concomitant Radiotherapy in patients with Vulval Cancer

Regimen details:

**Weeks 1 – 5 of Chemo-radiotherapy** (see Appendix 1):

**Chemotherapy:**
- **Cisplatin** 60mg/m² (max. 120mg) IV D1 and D29 (D1 of weeks 1and 5)
- **5-Fluorouracil (5-FU)** 1000mg/m²/24 hours IV D1–D4 and D29–D32 inclusive

**Radiotherapy (RT):**
- 50.4 Gy over 28 fractions (1.8 Gy/#) on Mondays to Fridays over 5 ½ weeks
  - OR
- 45 Gy over 25 fractions (1.8 Gy/#) on Mondays to Fridays over 5 weeks

**Radiotherapy (RT):** Radiotherapy is delivered over 5 – 5 ½ weeks on weekdays only, with concurrent chemotherapy during the first and fifth week. 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
- *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:** A single course of treatment, over 5 – 5 ½ weeks

**Extravasation:** Cisplatin and 5FU: Non-vesicants

**Anti- emetics:**
- D1: Highly emetogenic
- D2 – D4: Low emetogenic
- Follow Local Antiemetic Policy
Supportive medication: Patients may require:
- 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, Hb
- U&Es
- LFTs
- Mg²⁺ and Ca²⁺
- EDTA
- Audiogram
- Toxicity assessment (during RT)

Comments:
Haemoglobin level – Radiotherapy
Throughout the Radiotherapy treatment, Haemoglobin (Hb) should be maintained above 12g/dl. If the Hb falls below 12g/dl, a blood transfusion needs to be arranged (treatment may continue)

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.

DOSE MODIFICATIONS

Haematological Toxicity
WBC < 3.0 x 10^9/L
or
Neutrophils < 1.5 x 10^9/L
or
Platelets < 100 x 10^9/L
Consider 25% dose reduction in all drugs OR
Abandon chemotherapy at Consultant’s discretion
RT must continue

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 20% 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 60mg/m²</td>
</tr>
<tr>
<td>50 – 60</td>
<td>Give 50mg/m²</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Contraindicated</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>

Reason for Update: Network Protocol Development
Approved by Gynaecology Consultant: Anna Winship
Approved by SELCN DTAC Chair: Nic Ketley
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DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

NEUROPATHY/ OTOTOXICITY – CISPLATIN

Cisplatin induced neuropathy is cumulative:

<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 60mg/m²</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 50mg/m²</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>Omit Cisplatin, Continue 5-FU and RT</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Disabling</td>
<td>Omit Cisplatin, Continue 5-FU and RT</td>
</tr>
</tbody>
</table>

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

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
Appendix 1. Treatment summary

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<th>CHEMO-RADIOThERAPY</th>
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<tbody>
<tr>
<td><strong>Week</strong></td>
</tr>
<tr>
<td><strong>Days</strong></td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
</tr>
<tr>
<td>5-FU</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
</tbody>
</table>

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