Weekly Cisplatin plus Radiotherapy for Locally Advanced Cervical / Vaginal / Vulval Cancer

Indication: 1) Chemo-radiotherapy for patients with Locally Advanced Cervical / Vaginal / Vulval Cancer

2) Adjuvant Chemo-radiotherapy for high-risk patients post-surgery

Regimen details:

**Weeks 1 – 5 of Chemo-radiotherapy:**

Chemotherapy: Cisplatin 40mg/m² (max. 76mg) IV D1 q7

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

RT should ideally be given within one hour after Cisplatin infusion is completed, and definitely not more than 2 hours after chemotherapy (see Comments)

Administration: Furosemide 40mg orally

500ml Sodium Chloride 0.9% over 60 minutes

Cisplatin, in 500ml Sodium Chloride 0.9% IV over 60 minutes

1litre Sodium Chloride 0.9% + 20mmol KCl + 1g MgSO₄ IV infusion over 60 minutes

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

**If patient has significant nausea and vomiting, consider changing Cisplatin hydration schedule to long Hydration schedule for Cisplatin > 40mg/m² for subsequent cycles:

Furosemide 40mg orally

1litre Sodium Chloride 0.9% + 20mmol KCl + 1g MgSO₄ IV infusion over 60 minutes

Cisplatin, in 1000ml Sodium Chloride 0.9% IV over 2 hours

1litre Sodium Chloride 0.9% + 40mmol KCl + 1g MgSO₄ IV infusion over 2 hours

Then either 500ml Sodium Chloride 0.9% IV infusion over 60 minutes or 500ml drinking water

Frequency: Every 7 days, for 5 weeks

(*) A 6th cycle may be given in high-risk patients at Consultant's discretion

Extravasation: Cisplatin: Non-vesicant

Anti-emetics: Moderate emetogenic. Follow Local Anti-emetic Policy
Regular investigations:
- **FBC, Hb**: Weekly (see Comments)
- **U&Es**: Weekly
- **LFTs**: Weekly
- **Mg^{2+} and Ca^{2+}**: Weekly
- **EDTA**: Prior to 1st cycle (only if necessary)

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).

- **Cisplatin (radiosensitizer) – Radiotherapy**
  Since Cisplatin is used in this protocol as a radiosensitizer agent, it is to be administered on a day on which RT is delivered. If Radiation therapy is cancelled, do not give Cisplatin on that day and postpone chemotherapy until Radiation therapy resumes.

- **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 without Consultant approval.

- **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.

**DOSE MODIFICATIONS**

**Haematological Toxicity**

- **WBC < 3.0 x 10^9/L**
  - Delay Cisplatin for 1 week. Repeat FBC – If within normal parameters, proceed with 100% dose.
  - If patient has repeated delays, abandon chemotherapy at Consultant’s discretion.

- **Platelets < 100 x 10^9/L**

**Reason for Update:** Network Protocol Development

**Version:** 2

**Supersedes:** All other versions

**Date:** 15.01.10

**Prepared by:** M. Teresa Pacheca-Palomar

**Date:** Jan’10

**Checked by:** (Network Pharmacist): Jacky Turner

**Date:** 29.01.10

**Approved by SELCN DTAC Chair:** Nic Ketley

**Date:** 29.01.10
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% variation from baseline value, re-calculate GFR using the Cockcroft & Gault equation.

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>50 - 60</td>
<td>Continue therapy at full dose at Consultant’s discretion</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Hepatic Impairment: Cisplatin: No dose reduction necessary

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

PERIPHERAL 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 100%</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 100%</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</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Disabling</td>
<td>Omit Cisplatin</td>
</tr>
</tbody>
</table>

If toxicities occur with Cisplatin, it is NOT recommended to change to Carboplatin

Toxicities: Myelosuppression; fatigue; nausea; vomiting; constipation; diarrhoea; nephrotoxicity; neuropathy/ototoxicity; taste disturbance; electrolyte disturbances; allergic reactions

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, 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

References:

www.medicines.org.uk
SWSHCN – Approved Network regimen: Cisplatin + Radiotherapy. December 2008
COIN Guidelines. October 2000
Cisplatin dosage adjustment in Renal Impairment. Personal communication with Dr. A. Winship. Aug’09
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
CTCAE v3.0. August 2006

Appendix 1. Treatment summary

Weeks 1 – 5 of Chemo-radiotherapy:

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<table>
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<tr>
<th>CHEMO-RADIOTherAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
</tr>
<tr>
<td>Days</td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
</tbody>
</table>