Doxorubicin/Cisplatin in Advanced, Metastatic or Recurrent Endometrial Cancer

Indication: Palliative therapy for patients with Advanced, Metastatic or Recurrent Endometrial Cancer

Regimen details: Doxorubicin 60mg/m² (*) IV D1
Cisplatin 60mg/m² (*) IV D1

(*) Consider starting Doxorubicin and Cisplatin at 50mg/m² in patients with reduced performance status. Increase doses to 60mg/m² with second cycle only if well tolerated

Administration: Furosemide 40mg orally

**Doxorubicin**, IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion over 3 – 10 minutes
1litre Sodium Chloride 0.9% + 20mmol KCl + 1g MgSO₄ IV infusion over 60 minutes

**Cisplatin**, in 1litre 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

*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

Frequency: Every 21 days, for a maximum of 6 cycles

Extravasation: Doxorubicin: Vesicant
Cisplatin: Non-vesicant

Anti-emetics: Highly emetogenic. Follow Local Anti-emetic Policy

Regular investigations: FBC D1
U&Es D1
LFTs D1
Mg²⁺ and Ca²⁺ D1
CA – 125 D1
EDTA Prior to 1st cycle
Audiogram Prior to 1st cycle if clinically indicated
MUGA scan/Echocardiogram Prior to 1st cycle (see Comments)
CT scan (disease evaluation) After 3 cycles

Comments: Maximum cumulative dose Doxorubicin = 450 - 550mg/m²
A baseline MUGA scan or Echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, diabetes, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan or Echocardiogram 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 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

D1

WBC < 3.0 x 10^9/L
or
Neutrophils < 1.5 x 10^9/L
or
Platelets < 100 x 10^9/L

Delay therapy for 1 week. Repeat FBC – If within normal parameters, proceed with 100% doses.

Subsequent cycles

If Neutrophils < 0.5 x 10^9 / L for ≥ 7 days, OR
Febrile neutropenia is diagnosed OR
Platelets < 50 x 10^9/L,

Cisplatin and Doxorubicin doses should be reduced to 50mg/m^2 from previous doses. If the patient continues to experience these side effects at the lower doses, give 40mg/m^2. Discontinue therapy if there is no further improvement despite second dose reductions.

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 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>

Doxorubicin: Dose reduction in severe renal impairment (GFR < 10 ml/min) should be discussed with the Consultant

Hepatic Impairment

Cisplatin: No dose reduction necessary

Doxorubicin dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Doxorubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Give 100%</td>
</tr>
<tr>
<td>20 – 50</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>

<table>
<thead>
<tr>
<th>AST/ ALT (units)</th>
<th>Doxorubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3 x normal</td>
<td>Give 75%</td>
</tr>
</tbody>
</table>

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 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>Discontinue therapy</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Disabling</td>
<td>Discontinue therapy</td>
</tr>
</tbody>
</table>

If toxicities occur with Cisplatin, it is NOT recommended to change to Carboplatin.
Toxicities: Myelosuppression; fatigue; nausea; vomiting; constipation; diarrhoea; mucositis; nephrotoxicity; neuropathy/ ototoxicity; cardiotoxicity; taste disturbance; electrolyte disturbances; allergic reactions; alopecia

Drug interactions: Cisplatin
- Allopurinol, colchicine, probenecid, sulfipyrazone: 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

Doxorubicin
- Ciclosporin (high dose) increase Doxorubicin serum levels and myelotoxicity
- Concomitant use of other cardioactive compounds e.g. calcium channel blockers require monitoring of cardiac function throughout treatment
- Quinolones: antimicrobial effect of quinolones decreased
- Wafarin: the anticoagulant effect is increased

Doxorubicin and Cisplatin
- 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

References:
www.medicines.org.uk
COIN Guidelines. October 2000
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
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