Radiotherapy followed by Carboplatin / Paclitaxel in Endometrial Cancer

Indication: Adjuvant therapy in women with High Risk, Early Stage or Locally Advanced Endometrial Cancer

Radiotherapy

Regimen details:

Radiotherapy (RT) : 45 Gy over 25 fractions (1.8 Gy/#) on Mondays to Fridays over 5 weeks

Frequency: A single course of treatment over 5 weeks followed 4 weeks later by 4 cycles of Adjuvant Carboplatin / Paclitaxel

Followed by Carboplatin / Paclitaxel

Regimen details :
- Paclitaxel 175mg/m² IV D1
- Carboplatin AUC 5 IV D1 (see Comments)

Administration:
- **Paclitaxel** in 500mls Sodium Chloride 0.9% over 3 hours via non-PVC infusion bag, with a 0.22 micron in-line filter. Paclitaxel must be diluted to a concentration of 0.3-1.2mg/ml to maintain stability in clinical practice
- **Carboplatin** in 500mls Glucose 5% IV over 30-60 minutes

Any device containing aluminium that may come in contact with Carboplatin must be avoided

Premedication:
- Dexamethasone 20mg IV 30 – 60 minutes prior to Paclitaxel administration
- Chlorphenamine 10mg IV 30 – 60 minutes prior to Paclitaxel administration over at least 1 minute
- Ranitidine 50mg IV 30 – 60 minutes prior to Paclitaxel administration over at least 2 minutes

Frequency: Every 21 days, for 4 cycles

Extravasation: Paclitaxel: Vesicant
- Carboplatin: Non-vesicant

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

Regular investigations:
- FBC D1
- U&Es D1
- LFTs D1
- CA-125 D1
- EDTA Prior to 1st cycle, if necessary (see Comments)
Comments: Carboplatin dose should be calculated using the Calvert formula:
Dose = Target AUC x (25 + GFR)
GFR should be measured before the first cycle, by EDTA clearance or using the Cockcroft & Gault equation. Subsequent doses of Carboplatin should usually be based on this value of GFR.

If the calculated GFR < 60 or > 120ml/min, measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if the patient's serum Creatinine changes significantly (>20% from baseline value), recalculate GFR using the Cockcroft & Gault equation or measure EDTA clearance

DOSE MODIFICATIONS

Haematological Toxicity

Day 1

WBC < 3.0 x 10⁹/ L  or  Neutrophils < 1.5 x 10⁹/ L  or  Platelets < 100 x 10⁹/ L
  Delay for 1 week.
  Repeat FBC - If within normal parameters, resume treatment with Carboplatin and Paclitaxel at 100% doses

Subsequent cycles
If Neutrophils < 0.5 x 10⁹/ L for ≥ 7 days, OR
Febrile neutropenia is diagnosed OR
Platelets 50 x 10⁹/ L,
Dose reduce Paclitaxel to 135mg/m² and Carboplatin to AUC 4. If ongoing myelosuppression, despite the use of lower doses, discontinue therapy

Renal Impairment: Paclitaxel: No dose adjustment required. Assess renal function when clinically indicated Carboplatin: Contraindicated if CrCl < 20ml/min

Hepatic Impairment: Paclitaxel is not recommended in severe impaired hepatic function:

<table>
<thead>
<tr>
<th>AST / ALT (units)</th>
<th>Paclitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.5 x ULN</td>
<td>Give 100%</td>
</tr>
<tr>
<td>2.5 – 5 x ULN</td>
<td>Continue therapy at Consultant’s discretion</td>
</tr>
<tr>
<td>&gt; 5 x ULN</td>
<td>Discontinue therapy</td>
</tr>
</tbody>
</table>

Carboplatin: No dose adjustment required
DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

PERIPHERAL NEUROPATHY – PACLITAXEL

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neuropathy-sensory</th>
<th>Paclitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paresthesia (including tingling) but not interfering with function</td>
<td>Give 175mg/m²</td>
</tr>
<tr>
<td>2</td>
<td>Paresthesia interfering with function, but not interfering with activities of daily living</td>
<td>Reduce Paclitaxel dose to 135mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>Paresthesia interfering with activities of daily living</td>
<td>Discontinue therapy</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Discontinue therapy</td>
</tr>
</tbody>
</table>

ARTHRALGIA / MYALGIA – PACLITAXEL

Paclitaxel may cause Grade 1 or 2 arthralgia or myalgia:

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<thead>
<tr>
<th>Grade</th>
<th>Arthralgia/Myalgia</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Joint and muscle pain, not interfering with function</td>
<td>Consider use of NSAIDs</td>
</tr>
<tr>
<td>2</td>
<td>Joint and muscle pain, interfering with function, but not interfering with activities of daily living</td>
<td>Consider use of NSAIDs</td>
</tr>
</tbody>
</table>

Toxicities:
- Myelosuppression; fatigue; nausea; vomiting; constipation; diarrhoea; mucositis; nephrotoxicity; neurotoxicity / ototoxicity; myalgia / arthralgia; taste disturbance; hypersensitivity reactions (mainly flushing, rash and hypotension); alopecia

Drug interactions:
- Paclitaxel:
  - Concomitant administration of inducers or inhibitors of cytochrome P450 Isoenzymes (CYP2C8 and 3A4) e.g. erythromycin, fluoxetine, gemfibrozil, rifampicin, carbamazepine, phenytoin, phenobarbital etc, may alter the pharmacokinetics of Paclitaxel, presenting a theoretical interaction
  - Carboplatin:
    - Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
    - Clozapine: increased risk of agranulocytosis, avoid concomitant use
    - Diuretics: increased risk of nephrotoxicity and ototoxicity
    - Nephrotoxic drugs: increased nephrotoxicity; not recommended
    - Phenytoin: reduced absorption of the anti-epileptic
    - Warfarin: increased anticoagulant effect of warfarin

Reason for Update: Network Protocol Development
Approved by Gynaecology Consultant: Anna Winship
Supersedes: All other versions
Date: 08.09.09
Prepared by: Maria Teresa Pacheca-Palomar  Sept '09
Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley
Date: 20.10.09
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Appendix 1 Treatment summary

Radiotherapy for 5 weeks:

Radiotherapy (RT): 45 Gy over 25 fractions (1.8 Gy/#) on Mondays to Fridays over 5 weeks

Followed 4 weeks later by 4 cycles Chemotherapy

Chemotherapy: Paclitaxel 175mg/m² IV D1
Carboplatin AUC5 IV D1

<table>
<thead>
<tr>
<th>RADIOThERAPY</th>
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<tbody>
<tr>
<td>Week</td>
</tr>
<tr>
<td>Days</td>
</tr>
<tr>
<td>Radiotherapy</td>
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Followed 4 weeks later by 4 cycles of Chemotherapy:

<table>
<thead>
<tr>
<th>CHEMOTHERAPY (i.e. 2 cycles)</th>
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<tbody>
<tr>
<td>Week</td>
</tr>
<tr>
<td>Days</td>
</tr>
<tr>
<td>Paclitaxel</td>
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<tr>
<td>Carboplatin</td>
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