Carboplatin and Paclitaxel followed by Radiotherapy in Endometrial Cancer

**Carboplatin / Paclitaxel**

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

**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 – 6 cycles followed 4 weeks later by Radiotherapy (see page 3)

**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)
- **CT scan (disease evaluation)** After 3 cycles and 6 cycles if appropriate

**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), re-calculate 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>
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<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>
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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>
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</thead>
</table>
| 1     | Paresthesia (including tingling)  
  but not interfering with function | Give 175mg/m² |
| 2     | Paresthesia interfering with function,  
  but not interfering with activities of daily living | Reduce Paclitaxel dose to 135mg/m² |
| 3     | Paresthesia interfering with activities of daily living | Discontinue therapy |
| 4     | Disabling | Discontinue therapy |
ARTHRALGIA / MYALGIA – PACLITAXEL

Paclitaxel may cause Grade 1 or 2 arthralgia or myalgia:

<table>
<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 antiepileptic
- Warfarin: increased anticoagulant effect of warfarin

Followed by Radiotherapy

Radiotherapy should be started 4 weeks after the last administration of chemotherapy.

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

References:
- www.medicines.org.uk
- PORTEC – 3 Trial, CKTO 2006-04, CME P06.031, version 21 January 2008
- UCLH-Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
- UCLH-Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
- GSTT Guidelines for treating Nausea and Vomiting in adult patients. September 2007
- CTCAE v3.0. August 2006

Reason for Update: Network Protocol Development

| Version: 1 | Approved by Gynaecology Consultant: Anna Winship |
| Supersedes: All other versions | Date: 08.09.09 |
| Prepared by: Maria Teresa Pacheca-Palomar | Checked by (Network Pharmacist): Jacky Turner |
| Approved by SELCN DTAC Chair: Nic Ketley | Date: 20.10.09 |
Appendix 1 Treatment summary

Chemotherapy x 4 – 6 cycles:

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

Followed by Radiotherapy, starting 4 weeks after the last administration of Chemotherapy:

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

<table>
<thead>
<tr>
<th>CHEMOTHERAPY (i.e. 2 cycles)</th>
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<tbody>
<tr>
<td>Week</td>
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<tr>
<td>Days</td>
</tr>
<tr>
<td>Paclitaxel</td>
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<tr>
<td>Carboplatin</td>
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After 4 – 6 cycles of chemotherapy, 4 week gap then Radiotherapy:

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<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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