Paclitaxel and Carboplatin in Early-stage Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Indication: First line Adjuvant or Induction therapy in women with Early-stage Ovarian, Fallopian Tube and Primary Peritoneal 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: 21 days, 3 – 6 cycles

Extravasation: Paclitaxel: Vesicant
Carboplatin: Non-vesicant

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

Regular investigations: FBC D1
LFTs D1
U&Es D1
CA 125 Every 2 cycles
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), re-calculate GFR using the Cockcroft & Gault equation or measure EDTA clearance.
DOSE MODIFICATIONS

Haematological Toxicity

Day 1

In adjuvant treatment, dose reduction and delays can compromise outcome. G-CSF should be considered if more than one delay and/or before dose reduction. If in doubt, contact the relevant Consultant.

WBC < 3.0 x 10⁹/ L
  or
Neutrophils < 1.0 x 10⁹/ L
  or
Platelets < 100 x 10⁹/ L

Delay for 1 week.
Repeat FBC - If within normal parameters, resume treatment with Paclitaxel and Carboplatin 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 both drugs to Paclitaxel 135mg/m² and Carboplatin AUC 4 or seek Consultant advice and consider usage of G-CSF for following cycles. If the patient continues to experience these side effects at the lower dose, despite G-CSF usage, give Paclitaxel 105mg/m² and Carboplatin AUC 3 or consider omitting Paclitaxel and continuing Carboplatin at full dose i.e AUC 5

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>Bilirubin (µmol/L)</th>
<th>Paclitaxel Dose (mg/m²)</th>
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<tbody>
<tr>
<td>&lt; 26</td>
<td>135</td>
</tr>
<tr>
<td>27 – 51</td>
<td>75</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>50</td>
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</tbody>
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Carboplatin: No dose adjustment required

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

PERIPHERAL NEUROPATHY – PACLITAXEL

Grade | Neuropathy-sensory | Paclitaxel Dose |
-------|------------------|----------------|
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 | Omit Paclitaxel |
4      | Disabling | Omit Paclitaxel |
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: anaemia; leukopenia; neutropenia; infection; thrombocytopenia; fatigue; nausea; vomiting; mucositis; diarrhoea; constipation; dysgeusia; hypersensitivity reactions (mainly flushing, rash and hypotension); peripheral neuropathy; alopecia; arthralgia; myalgia

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

References:
- www.medicines.org.uk
- Barnias et al. BMC Cancer (2006);6:228
- 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