Paclitaxel 80 and Carboplatin AUC 2 in Advanced Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Indication: Second or subsequent line Palliative therapy in women with Advanced Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Regimen details: Paclitaxel 80mg/m\(^2\) IV D1, D8, D15
Carboplatin AUC 2 IV D1, D8, D15 (see Comments)

Administration: Paclitaxel in 250mls Sodium Chloride 0.9% over 1 hour 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 250mls Glucose 5% IV over 30-60 minutes
Any device containing aluminium that may come in contact with Carboplatin must be avoided

Premedication: Dexamethasone 8mg 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 28 days, for 6 cycles

Extravasation: Paclitaxel: Vesicant
Carboplatin: Non-vesicant

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

Regular investigations: FBC D1,D8,D15
LFTs D1
U&Es D1
CA 125 Every cycle
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

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

Delay for 1 week.

or Repeat FBC - If within normal parameters, resume treatment with Paclitaxel and Carboplatin at 100% doses

Day 8 and Day 15

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Platelets</th>
<th>Paclitaxel/Carboplatin doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 x 10^9/L</td>
<td>≥ 100 x 10^9/L</td>
<td>Give 100%</td>
</tr>
<tr>
<td>1.0 – 1.49 x 10^9/L</td>
<td>75 – 99 x 10^9/L</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 1.0 x 10^9/L</td>
<td>&lt; 75 x 10^9/L</td>
<td>Omit doses. Do NOT delay</td>
</tr>
</tbody>
</table>

Renal Impairment: Paclitaxel: No dose adjustment required
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>
</tr>
</thead>
<tbody>
<tr>
<td>22 – 26</td>
<td>Give 75 – 80%</td>
</tr>
<tr>
<td>27 – 51</td>
<td>Give 40 – 45%</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>Give 30%</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 80mg/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 65mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>Paresthesia interfering with activities of daily living</td>
<td>Omit Paclitaxel</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Omit Paclitaxel</td>
</tr>
</tbody>
</table>

Reason for Update: Network Protocol Development
Approved by Gynaecology Consultant: Ana Montes
Supersedes: All other versions Date: 17.03.10
Prepared by: M. Teresa Pacheca-Palomar Jan’10 Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley Date: 26.04.10
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>

NON – HAEMATOLOGICAL TOXICITY

For any other Grade 3 – 4 toxicity, treatment should be deferred until recovery, and then continued with an appropriate dose reduction. Discuss with Consultant

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
Katsumata N et al. Lancet 2009 Sept 18; Epub ahead of print
Safra T et al. Gynecologic Oncology (2009); Vol 114 (2): 215 - 218
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