Pegylated liposomal Doxorubicin (Caelyx) and Carboplatin in Ovarian carcinoma, 2nd line

Indication: Second line treatment option in platinum sensitive Ovarian cancer
- Histologically confirmed cancer of the Ovary, fallopian tube or primary peritoneal cancer
- Previous response to platinum based chemotherapy and disease relapse after a period of more than 6 months after completion of first line therapy
- Previous exposure to taxane chemotherapy or underlying contraindication or allergy to taxane based treatment
- ECOG performance status 0 to 2
- Adequate cardiac function

Regimen details:
Pegylated Liposomal Doxorubicin (Caelyx) 30mg/m² IV D1
Carboplatin AUC 5 (see Comments) IV D1

Administration:
Caelyx, by infusion in 5% Dextrose:
- Caelyx dose < 90mg Dilute in 250mls 5% Dextrose
- Caelyx dose ≥ 90mg Dilute in 500mls 5% Dextrose
*Caelyx is incompatible with Sodium Chloride. The IV line should be flushed before and after the infusion with 5% Dextrose

Carboplatin in 500mls Glucose 5% IV over 30 – 60 minutes

*The initial Caelyx dose should be administered no faster than 1mg/minute, to minimize the risk of infusion reactions. If no infusion reaction occur with the first dose, subsequent Caelyx infusions may be administered over 1 hour
In those patients who experience an infusion reaction, stop temporarily the infusion until symptoms have cleared with or without further therapy (antihistamines, corticosteroids, adrenaline) and resume treatment, at a slower rate, as follows:
5% of the total dose should be infused slowly over the first 15 minutes
If tolerated, without reaction: may double the infusion rate for the next 15 minutes
If tolerated: complete the infusion over the next hour for a total infusion time of 90 minutes

Frequency: Every 28 days, up to 9 cycles

Extravasation:
Caelyx: Non - Vesicant
Carboplatin: Non- vesicant

Anti- emetics: Moderate emetogenicity
Follow Local Anti-emetic Policy

Regular investigation:
- FBC D1
- LFTs D1
- U&Es D1
- CA 125 Every 2 cycles
- EDTA Prior to 1st cycle
- ECHO/MUGA Baseline & as required (see comments)
Carboplatin: The total dose should be calculated in milligrams, using the Calvert formula:
\[ \text{Dose} = \text{Target AUC} \times (25 + \text{GFR}) \]
GFR should be measured before the first cycle, by EDTA clearance. Subsequent doses of Carboplatin should usually be based on this value of GFR.
Monitor trends in serum creatinine between treatments: if the patient’s serum Creatinine changes significantly (>20% from baseline value), measure EDTA clearance.

Maximum cumulative dose Caelyx = 450 – 550mg/m²
Consider previous anthracycline exposure

A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum.

Supportive medication: Emollients and Pyridoxine 50mg po TDS for Palmar-Plantar Erythrodysesthesia (not scientifically proven)

Toxicities: Myelosuppression, Palmar-Plantar Erythrodysesthesia, fatigue, nausea, vomiting, mucositis, dysgeusia, hypersensitivity reactions, constipation, diarrhoea, cardiotoxicity, anorexia, asthenia, potential alopecia

DOSE MODIFICATIONS

Haematological toxicity

Neutrophils < 1.0 x 10⁹/L
or
Platelets < 100 x 10⁹/L
Delay for 1 week.

Neutrophils < 0.5 x 10⁹/L for ≥ 7 days, OR
Febrile Neutropenia is diagnosed OR
Platelets < 50 x 10⁹/L, or bleeding requiring platelet transfusion

Reduce Carboplatin dose by 1 x AUC from previous dose (do not escalate for subsequent cycles) or seek Consultant advice. If the patient continues to experience these side effects at the lower dose, decrease Carboplatin dose by 2 x AUC

Renal Impairment

Carboplatin: Contraindicated if CrCl < 20ml/min
Hepatic Impairment  
Carboplatin: No dose adjustment required  
Caelyx dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Caelyx Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 50</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

Cutaneous toxicity (Caelyx):

<table>
<thead>
<tr>
<th>TOXICITY GRADE After Prior Caelyx Dose</th>
<th>PALMAR-PLANTAR ERYTHRODYSESTHESIA</th>
<th>STOMATITIS</th>
<th>WEEK 4 After Prior Caelyx Dose</th>
<th>WEEK 5 After Prior Caelyx Dose</th>
<th>WEEK 6 After Prior Caelyx Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild erythema, swelling or Desquamation not interfering with ADL</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>Redose unless patient experienced a previous Grade 3 or 4 toxicity, in which case wait an additional week</td>
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<td>Give 20mg/m² or stop treatment-discuss with Consultant</td>
</tr>
<tr>
<td>2</td>
<td>Erythema, desquamation or swelling interfering with but not precluding normal physical activities; small blisters or ulcerations &lt; 2cm in diameter</td>
<td>Painful erythema, oedema or ulcers, but can eat</td>
<td>Wait an additional week</td>
<td>Wait an additional week</td>
<td>Give 20mg/m² or stop treatment-discuss with Consultant</td>
</tr>
<tr>
<td>3</td>
<td>Blistering, ulceration or swelling interfering with walking or normal daily activities; cannot wear usual clothing</td>
<td>Painful erythema, oedema or ulcers, but cannot eat</td>
<td>Wait an additional week</td>
<td>Wait an additional week</td>
<td>No further treatment</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse or local process causing infectious complications, or a bedridden state or hospitalisation</td>
<td>Requires parenteral or enteral support</td>
<td>Wait an additional week</td>
<td>Wait an additional week</td>
<td>No further treatment</td>
</tr>
</tbody>
</table>

The following measures may help to minimise the risk of PPE for the first 4 – 7 days after Caelyx infusion:  
Keep hands and feet as cool as possible  
Do not wear tight fitting gloves or socks and avoid wearing tight-fitting footwear and high heeled shoes  
Avoid exposing the skin to very hot water, such as the bath or washing up  
Do not rub the skin vigorously or use abrasive washcloths. Pat skin dry after washing  
Avoid the use of topical anaesthetics as they can worsen skin reactions
Drug interactions:

Caelyx:
- Ciclosporin (high dose) increase Caelyx serum levels and myelotoxicity
- Concomitant use of other cardioactive compounds e.g. calcium channel blockers require monitoring of cardiac function throughout treatment
  -- Phenytoin: reduced blood levels of the anticonvulsant and increased seizure activity
- Warfarin: the anticoagulant effect is increased

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
Pujade-Lauraine E. et al. JCO (2010); 28(20):3323-3329