GEMCITABINE/CARBOPLATIN (+/- Bevacizumab) in Advanced Ovarian Cancer

Indication: Second line palliative therapy in platinum sensitive patients with ovarian, fallopian tube or primary peritoneal cancer unable to tolerate paclitaxel
Or in combination with bevacizumab as per NCDF criteria

Regimen details: Gemcitabine 1000mg/m² IV D1 and D8
Carboplatin AUC 5 IV D1
Note: use carboplatin AUC 4 when prescribed concomitantly with bevacizumab
(See separate protocol for bevacizumab second-line)

Administration: Gemcitabine in 250ml sodium chloride 0.9% over 30 minutes
Carboplatin in 500ml Glucose 5% IV over 1 hr

Frequency: 3 weekly cycle, for 6 cycles

Extravasation: Non-vesicant

Anti- emetics: Day 1: High emetogenicity
Day 8. Mild emetogenicity
Follow local anti-emetic policy

Regular investigations: FBC D1 and D8
LFTs D1
U&Es D1
EDTA Prior to 1st cycle, only if indicated (see comments)
Ca125 prior to each cycle
Disease evaluation every 3 cycles

Comments: Carboplatin dose should be calculated using the Calvert formula:
Dose = Target AUC x (25 + GFR)
GFR should be calculated using the Cockcroft & Gault equation in all patients; if the calculated GFR < 60 or >120ml/min, measure EDTA clearance before prescribing.
Monitor trends in serum creatinine between treatments; if >25% from baseline value re-calculate GFR using the Cockcroft & Gault equation.

Toxicities: Myelosuppression, anaemia, fatigue, nausea, vomiting, mucositis, flu-like syndrome, elevation of transaminases, proteinuria, haematuria, peripheral oedema, dyspnoea, hypersensitivity reactions, skin rash, alopecia (mild).

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 100% doses*
* Gemcitabine should be given at 75% dose and carboplatin should be reduced by 1 x AUC if:
  - If Neutrophils < 0.5 x 10^9/L for more than 7 days OR
  - Febrile neutropenia is diagnosed OR
  - Platelets < 50 x 10^9/L

Do not escalate doses for subsequent cycles.

<table>
<thead>
<tr>
<th>Day 8</th>
<th>Neutrophils</th>
<th>Platelets</th>
<th>Gemcitabine dose</th>
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<tbody>
<tr>
<td></td>
<td>≥ 1.0 x 10^9/L</td>
<td>and</td>
<td>Give 100% dose</td>
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<tr>
<td></td>
<td>05 – 0.99 x 10^9/L</td>
<td>and/or</td>
<td>Give 75% dose</td>
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<tr>
<td></td>
<td>&lt;0.5 x 10^9/L</td>
<td>and/or</td>
<td>Omit (do not defer)</td>
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Renal Impairment: Gemcitabine: consider dose reduction if GFR <30ml/min – discuss with consultant
Carboplatin: contra-indicated if GFR <20ml/min

Hepatic Impairment: Gemcitabine:
Use with caution in the presence of hepatic dysfunction. Administration of gemcitabine in patients with liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency:
  - If bilirubin >27 μmol/L, initiate treatment with gemcitabine 800mg/m²
  - If bilirubin >30 μmol/L or ALT/ALP >3 x ULN (>5 x ULN if liver metastases present), treatment should be deferred unless approved by the consultant. These patients are at high risk of potentially fatal sepsis.

Carboplatin: no dose reduction necessary

Non-Haematological Toxicities:
In case of grade 3 or 4 toxicity, treatment should be deferred until recovery, and then continued with an appropriate dose reduction – discuss with the consultant

Haemolytic anaemia
Gemcitabine should be discontinued at the first signs of any evidence of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of haemolytic uraemic syndrome. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required

Drug interactions:
Gemcitabine:
Gemcitabine is radiosensitiser
Warfarin – increased anticoagulant effect of warfarin

Carboplatin:
Aminoglycoside antibiotics - increased risk of nephrotoxicity and ototoxicity
Diuretics - increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs - increased nephrotoxicity – not recommended
Phenytoin – reduced absorption of phenytoin
Aluminium – forms black precipitate – do not use for preparation or administration
Warfarin – increased anticoagulant effect of warfarin
Clozapine – increased risk of agranulocytosis, avoid concomitant use

Reason for Update: update AUC when used with bevacizumab
Approved by Consultant: Ana Montes
Version: 2 Date: 12/7/13
Supersedes: version 1 Checked by (Principal Pharmacist):
Prepared by: Lisa Yuen 05Jun2013 Date: 18/7/13
References: