Breast Pathway Group – Gemcitabine & Carboplatin in Advanced Breast Cancer

**Indication:** Palliative therapy for triple negative advanced breast cancer

**Regimen details:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1000mg/m²²</td>
<td>IV</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Carboplatin*</td>
<td>AUC 5* (EDTA)</td>
<td>IV</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

*Carboplatin dose is calculated using the Calvert formula:
Dose = Target AUC x (25 + GFR)

Gold standard GFR is measured using EDTA wherever possible. If not available, Cockcroft & Gault equation may be used to estimate GFR for the first cycle; if the calculated GFR <60 or >120ml/min measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if >25% from baseline value re-calculate GFR using the Cockcroft & Gault equation.

Due to haematological toxicity, starting doses may be reduced in heavily pre-treated patients:

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<td>800mg/m²²</td>
<td>IV</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 4</td>
<td>IV</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

**Administration:**

- Gemcitabine in 100-500ml Sodium Chloride 0.9% IV over 30 min
- Carboplatin in 250-500ml Glucose 5% IV over 1 hour

Carboplatin infusion-related hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, dyspnoea and fever or chills following the start of the infusion; the infusion should be slowed down or interrupted and the necessary supportive medication should be administered. Severe reactions such as hypotension and/or bronchospasm or generalised rash/erythema requires immediate discontinuation. Availability of resuscitation equipment must be ensured as a standard precaution.

**Frequency:** Day 1 & 8, every 21 days, for 6 cycles
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Pre-medications: Paracetamol / Chlorphenamine / Hydrocortisone can be given for infusion-related reactions such as chills / fever

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

Supportive medication: Mouthcare as per local policy

Extravasation: Gemcitabine – Non-vesicant  
Carboplatin – Irritant

Regular investigations:

Prior to Cycle 1:
- EDTA  
- FBC  
- LFTs  
- U&Es

Prior to Day 8 (all cycles):
- FBC

Prior to Day 1 (all cycles):
- FBC  
- LFTs  
- U&Es

Toxicities: Myelosuppression (particularly thrombocytopenia), fatigue, alopecia (mild), mucositis, somnolence, proteinuria and haematuria, allergic skin rashes, oedema, asthenia, rarely pneumonitis, elevation of transaminases, neurotoxicity (ototoxicity), nephrotoxicity, infertility/ovarian failure

DOSE MODIFICATIONS

Haematological Toxicity

Day 1

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 &amp; ≥ 100</td>
<td>&amp;</td>
<td>100% dose</td>
</tr>
</tbody>
</table>
| < 1.5 or < 100 | or | Delay for 1 week.  
Repeat FBC – if recovered to above these levels, resume treatment with 100% dose. Consider dose reduction for > 1 delay |

Version: 1.0  
Supersedes: all other versions
Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014

Reason for Update: LCA Protocol Development
Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl

Prepared by: Wendy Ng
Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson

Second check by: Lisa Yuen
Date prepared: November 2014  
Review Date: November 2016

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.  
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Dose reduction and / or delay is more appropriate in the advanced setting.
- If during the preceding cycle, the patient has experienced neutrophils < 0.5 x 10^9/L or has febrile neutropenia diagnosed, GCSF should be considered.
- If platelets persistently < 100 x 10^9/L on Day 1 despite dose delay – seek Consultant advice and consider dose reduction by 25%

Prior day 8 – Gemcitabine

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0</td>
<td>&amp;</td>
<td>100% dose</td>
</tr>
<tr>
<td>0.5 – 0.9</td>
<td>or</td>
<td>75% dose</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>or</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Re-assess on day 1 of the next cycle

Non-haematological Toxicities

Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Gemcitabine Dose</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30ml/min</td>
<td>100%</td>
<td>Contra-indicated if GFR &lt;20ml/min.</td>
</tr>
<tr>
<td>&lt; 30ml/min</td>
<td>Gemcitabine should be used with caution in patients with CrCl &lt;30ml/min; however, no specific dosing recommendations have been made.</td>
<td>&lt; 30ml/min</td>
</tr>
</tbody>
</table>

Hepatic Impairment

<table>
<thead>
<tr>
<th>Hepatic Impairment</th>
<th>Gemcitabine Dose</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST elevations do not seem to cause dose limiting toxicities If bilirubin &gt;27μmol/L, initiate treatment with 800mg/m²</td>
<td>Probably no dose reduction necessary</td>
<td></td>
</tr>
</tbody>
</table>
Dose modifications for other toxicities as appropriate

In case of grade 3 or 4 neurotoxicity, Carboplatin should be discontinued.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Stomatitis</th>
<th>Diarrhoea</th>
<th>Dose Reductions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>Increase of 2-3 stools/day or mild increase in loose watery colostomy output</td>
<td>100% doses</td>
</tr>
<tr>
<td>2</td>
<td>Painful erythema, edema, or ulcers but can eat</td>
<td>Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output</td>
<td>Omit until resolved, then resume at 100% doses</td>
</tr>
<tr>
<td>3</td>
<td>Painful erythema, edema, or ulcers and cannot eat</td>
<td>Increase of 7-9 stools/day or incontinence, malabsorption, or severe increase in loose watery colostomy output</td>
<td>Omit until resolved, then resume gemcitabine at 75% dose and carboplatin at 75% dose</td>
</tr>
<tr>
<td>4</td>
<td>Mucosal necrosis, requires parenteral support</td>
<td>Increase of 10 or more stools/day or grossly bloody diarrhoea, or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support, dehydration</td>
<td>Omit until resolved, then resume gemcitabine at 50% dose and carboplatin at 75% dose</td>
</tr>
</tbody>
</table>

Location of regimen: Outpatient setting

Availability of resuscitation equipment must be ensured as a standard precaution.

Comments:

**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 is radiosensitiser
  - Warfarin - increased risk of bleeding (Gemcitabine)
  - Phenytoin – Carboplatin decreases efficiency
  - Nephrotoxic drugs (with Carboplatin)
  - Aminoglycoside antibiotics-increased risk of ototoxicity (with Carboplatin)

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References:
- Mount Vernon Gem/carbo protocol
- NWLCN Breast Regimen Version 7 01
- Summary of product characteristics – gemcitabine, carboplatin available at www.medicines.org.uk
- LCA Breast Cancer Clinical Guidelines October 2013