Lung Pathway Group – Gemcitabine & Carboplatin in Non-Small Cell Lung Cancer (NSCLC)

Indication: First line treatment option in advanced or metastatic NSCLC
Induction therapy prior to definitive irradiation in stage IIIA / IIIB

Regimen details:
Gemcitabine 1250 mg/m² IV Days 1 and 8
Carboplatin AUC 5 (EDTA) IV Day 1

Administration:
Day 1
Gemcitabine in 250 - 500ml Sodium Chloride 0.9% IV over 30 minutes
Carboplatin in 500ml Glucose 5% IV over 60 minutes.

Aluminium containing equipment should not be used during preparation and administration of carboplatin

Day 8
Gemcitabine in 250 - 500ml Sodium Chloride 0.9% IV over 30 minutes

Hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills, usually during the first and second infusions and within a few minutes 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 and 8, every 21 days for 4 to 6 cycles.

Pre-medication: Not routinely required
Anti-emetics: Day 1: High emetogenicity
Day 8: Low emetogenicity
Follow local anti-emetic policy

Supportive medication: Mouthcare as per local policy
Paracetamol / Chlorphenamine / Hydrocortisone can be given for administration-related reactions such as chills / fever.

Extravasation: Non-vesicant

Regular investigations:
- Prior to Cycle 1:
  - FBC Day 1 (within 14 days)
  - LFTs Day 1 (within 14 days)
  - U&Es Day 1 (within 14 days)
  - CT scan Baseline
  - EDTA See comments

Comments:
Carboplatin dose should be calculated using the Calvert formula: Dose = Target AUC x (25 + GFR). GFR should be calculated using EDTA clearance before prescribing. (If EDTA not available prior to cycle 1, initiate treatment using the Cockcroft & Gault formula to calculate GFR, and ensure EDTA prior to cycle 2). Monitor trends in serum creatinine between treatments, if >25% from baseline value re-calculate GFR using the Cockcroft & Gault formula or EDTA.

- Prior to Day 8 (all cycles):
  - FBC Day 8 (within 48 hours)
- Prior to Day 1 (all cycles):
  - FBC Day 1 (within 72 hours)
  - LFTs Day 1 (within 72 hours)
  - U&Es Day 1 (within 72 hours)
  - Imaging After 3 cycles

Toxicities: Myelosuppression, skin rash, alopecia (mild), mucositis, diarrhoea, neurotoxicity (including ototoxicity), nephrotoxicity, ovarian failure/infertility, nausea/vomiting.
**DOSE MODIFICATIONS**

**Haematological Toxicity**

**Prior to day 1**

<table>
<thead>
<tr>
<th>Neutrophils (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 &amp; ≥ 100</td>
<td></td>
<td>100% dose</td>
</tr>
<tr>
<td>&lt; 1.5 &amp;/or &lt; 100</td>
<td></td>
<td>Delay for 1 week. Repeat FBC, if recovered above these levels give 100% dose.</td>
</tr>
</tbody>
</table>

If neutrophils < 0.5 x 10⁹/L for more than 5 days or < 0.1 x 10⁹/L for more than 3 days, or platelets < 25 x 10⁹/L, or febrile neutropenia is diagnosed, or toxicity related delay is > 1 week - gemcitabine dose should be reduced to 75% from previous dose (do not escalate for subsequent cycles).

**Prior day 8**

<table>
<thead>
<tr>
<th>Neutrophils (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.0 &amp; &gt; 100</td>
<td></td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>0.5 – 0.9 or 75 – 99</td>
<td></td>
<td>Give 75% dose Dose can be re-escalated in subsequent cycles, providing the FBC has returned to normal limits.</td>
</tr>
<tr>
<td>&lt; 0.5 or &lt; 75</td>
<td></td>
<td>Omit Re-assess on day 1 of the next cycle</td>
</tr>
</tbody>
</table>

**Non-haematological Toxicities**

**Renal Impairment**

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Gemcitabine Dose</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30</td>
<td>Give 100% dose</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Use with caution, no specific dosing recommendations available</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>&lt; 20</td>
<td></td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

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**Hepatic Impairment**

**Carboplatin**  
No dose modifications required

**Gemcitabine**  
Use gemcitabine with caution in the presence of hepatic dysfunction. In clinical trials, gemcitabine was associated with transient elevations of serum transaminases in approximately 70% of patients. However, there is no evidence that longer duration of gemcitabine exposure or greater total cumulative gemcitabine dose increases hepatic toxicity. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency.

<table>
<thead>
<tr>
<th>Bilirubin (μmol/L)</th>
<th>ALT or ALP</th>
<th>Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 27 and ≤ 30</td>
<td></td>
<td>Give 800mg/m²</td>
</tr>
<tr>
<td>&gt; 30 or &gt; 3 x ULN</td>
<td>&gt; 3 x ULN (or &gt; 5 x ULN if liver metastases present)</td>
<td>Withhold and seek consultant advice – high risk of sepsis</td>
</tr>
</tbody>
</table>

**Dose modifications for other toxicities**

**Neurotoxicity**

<table>
<thead>
<tr>
<th>Neurotoxicity</th>
<th>Gemcitabine Dose</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Give 100% dose</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**Other toxicities**

<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>Give 100% doses</td>
</tr>
</tbody>
</table>
| 2     | Painful erythema, edema, or ulcers but can eat  | Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output | Omit until resolved, then resume at 100% doses  
For 2nd occurrence, resume at 75% doses |
| 3     | Painful erythema, edema, or ulcers and cannot eat | Increase of 7-9 stools/day or incontinence, malabsorption, or severe increase in loose watery colostomy output | Omit until resolved, then resume at 75% doses |
| 4     | Mucosal necrosis, requires parenteral support   | Increase of 10 or more stools/day or grossly bloody diarrhoea, or grossly bloody colostomy output | Omit until resolved, then resume at 50% doses  
(except for mucositis – give |
or loose watery colostomy output requiring parenteral support, dehydration

Doses reduced for toxicity should not be re-escalated

Location of regimen: Day case setting

Comments:

**Haemolytic anaemia – Gemcitabine**

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.

Women of childbearing potential must use effective contraception during treatment.

Sexually mature males are advised not to father a child during the treatment, and up to 6 months thereafter. If appropriate, male patients should be advised to seek counselling on sperm storage before starting treatment.

**Drug interactions:**

Gemcitabine is radiosensitiser

- Warfarin - increased risk of bleeding (Gemcitabine)
- Phenytoin – Carboplatin decreases efficiency
- Nephrotoxic drugs (with Carboplatin)

**References:**