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

Indication:
First line in radical/induction treatment in locally advanced NSCLC
First line palliative treatment in advanced/metastatic NSCLC

Regimen details:
Carboplatin  AUC 5 (EDTA)  IV  Day 1
Vinorelbine  25 - 30mg/m² (max 60mg)  IV  Day 1 and Day 8

Concomitant with radiotherapy*:
Carboplatin  AUC 2  IV  Day 1
Vinorelbine  15mg/m² (max 30mg)  IV  Day 1 and Day 8

*When combined with radiotherapy, vinorelbine and carboplatin dose are reduced. 2 or 3 cycles of radiotherapy may be given concomitantly with chemotherapy, continue with full dose chemotherapy after radiotherapy is completed to total of 4 cycles of treatment.

Administration:
Day 1
Vinorelbine in 50ml infusion bag of Sodium Chloride 0.9% over 5-10 minutes, via fast running infusion of Sodium Chloride 0.9%
Carboplatin in 500ml Glucose 5% over 60 minutes.

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

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.

Day 8
Vinorelbine in 50ml infusion bag of 0.9% Sodium Chloride over 5-10 minutes, via fast running infusion of Sodium Chloride 0.9%

Frequency: Day 1 and Day 8, every 21 days

Induction/adjuvant Total of 4 cycles; 2 to 3 cycles may be given concomitantly with radiotherapy

Advanced/palliative Total of 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: Carboplatin is non-vesicant
Vinorelbine is vesicant

Vinorelbine should be administered with appropriate precautions to prevent extravasation.
If there is any possibility that extravasation has occurred, contact a senior member of the medical team and follow local protocol for dealing with cytotoxic extravasation

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)
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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

*Imaging not required in adjuvant setting

Toxicities:
Myelosupression, ovarian failure/infertility, peripheral neuropathy and neuropathy induced constipation, alopecia (usually mild), GI symptoms, nausea and vomiting, myalgia, fatigue, neurotoxicity (ototoxicity), nephrotoxicity, encephalopathy, electrolyte imbalances.

DOSE MODIFICATIONS

Haematological Toxicity

Prior to day 1

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Carboplatin Dose</th>
<th>Vinorelbine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 &amp; ≥ 100</td>
<td></td>
<td>100% dose</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 to above these levels give 100% dose.</td>
<td>Delay for 1 week. Repeat FBC, if recovered to above these levels give 100% dose.</td>
</tr>
</tbody>
</table>

If neutrophils < 0.5 x 10^9/L for more than 5 days or < 0.1 x 10^9/L for more than 3 days, or platelets < 25 x 10^9/L, or febrile neutropenia is diagnosed, or toxicity related delay is > 1 week
- vinorelbine dose should be reduced to 75% from previous dose (do not escalate for subsequent cycles).

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Prior day 8

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

Non-haematological Toxicities

Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Vinorelbine: Dosage adjustment not required

Hepatic Impairment

Carboplatin: No dose modifications required

Vinorelbine:
If hepatic insufficiency is due to metastatic involvement, liver function may recover in response to treatment. Therefore, for patients with massive liver metastases, i.e. >75% of liver volume replaced by tumour, it is empirically suggested that the dose of vinorelbine be reduced to 85% dose and haematological toxicity closely followed up.

If hepatic insufficiency is due to other reasons, the table below should be used:

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>ALT / AST</th>
<th>Vinorelbine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5 x ULN</td>
<td>&lt; 5 x ULN</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>1.5 – 3 x ULN</td>
<td>5 – 20 x ULN</td>
<td>Delay day 1 for 1 week/omit day 8, and reassess*. Consider dose reduction to 25-50% dose.</td>
</tr>
<tr>
<td>&gt; 3 x ULN</td>
<td>&gt; 20 x ULN</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

*If liver toxicity persists for more than 3 weeks, discontinue treatment

Dose modifications for other toxicities

Neurotoxicity

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

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## Other toxicities

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin Dose</th>
<th>Vinorelbine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 mucositis</td>
<td>Give 100% of previous dose</td>
<td>Give 75% of previous dose</td>
</tr>
<tr>
<td>Grade 4 mucositis</td>
<td>Give 75% of previous dose</td>
<td>Give 50% of previous dose</td>
</tr>
<tr>
<td>Any grade 3 toxicities (except mucositis),</td>
<td>Give 75% of previous dose</td>
<td>Give 75% of previous dose</td>
</tr>
<tr>
<td>Any grade 4 toxicities (except mucositis)</td>
<td>Give 50% of previous dose</td>
<td>Give 50% of previous dose, or omit if Day 8 dose</td>
</tr>
<tr>
<td>Diarrhoea (any grade) requiring hospitalisation</td>
<td>Give 75% of previous dose</td>
<td>Give 75% of previous dose</td>
</tr>
<tr>
<td>Grade 3 oesophagitis with radiotherapy</td>
<td>Delay for 1 week, continue radiotherapy if possible</td>
<td>Omit – consider substituting with gemcitabine</td>
</tr>
<tr>
<td>Grade 3 or 4 constipation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If patient suffers any Grade 3 or 4 toxicity after 2 dose reductions, treatment must be reviewed by consultant.

**Location of regimen delivery:**
- **Day case setting**

**Comments:**
- 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:**
- Itraconazole- increased risk of neurotoxicity
- Posaconazole, voriconazole- increased vinorelbine plasma levels
- Omeprazole and fluoxetine may inhibit vinorelbine metabolism
- Phenytoin – carboplatin decreases efficiency
- Nephrotoxic drugs (with carboplatin)

**References:**
- [www.medicines.org.uk](http://www.medicines.org.uk)
- Cremonesi *et al.* Oncology 2003; 64(2): 97-101