REGIMEN TITLE: Carboplatin Vinorelbine (Oral) therapy

Indication: Induction, Adjuvant and Advanced & Palliative treatment of Non-small cell lung cancer patients when Cisplatin is not suitable treatment option

Eligible for patients able to tolerate and comply with oral dosage forms.

Regimen details: Carboplatin AUC 5(see comments) IV D1
(Carboplatin AUC 6 if dose calculated using Cockroft&Gault equation for GFR)
Vinorelbine 60mg/m² PO D1 and D8 First cycle
*Vinorelbine 80mg/m² PO D1 and D8 Second cycle onwards

(* See dose escalation guidance under ‘Dose modifications’ section-
Note: Vinorelbine dose escalation is not indicated in advanced disease or palliative treatment intention, unless vinorelbine is used as monotherapy)

See Appendix1. for Vinorelbine dosing table according BSA

Administration: Carboplatin in 500ml Glucose 5% IV over 60 minutes
Vinorelbine:
Vinorelbine is available as 20mg, 30mg and 80mg soft capsules.
Capsules to be swallowed with water without chewing or sucking the capsule.
Capsules are recommended to be taken with food.
Day one vinorelbine dose to be taken in the clinic before carboplatin administration.

Frequency: 3 weekly cycle
Induction/ Adjuvant Total of 4 cycles
Advanced/ palliative Total of 4-6 cycles

Anti- emetics: Day 1. Highly emetogenic
Day 8. Mildly/ moderately emetogenic

Extravasation: Carboplatin- non vesicant
Vinorelbine PO- not applicable

Regular investigations:
FBC D1 and D8
LFTs D1
U&Es D1
EDTA Prior to 1st cycle (see Comments)
Baseline CT
Clinical toxicity assessments (including neuropathy & local toxicity)

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 or creatinine clearance before prescribing. Carboplatin dose is calculated as AUC5 if EDTA is used. Monitor
trends in serum creatinine between treatments: if >25% from baseline value re-calculate GFR using the Cockcroft & Gault equation.

Adequate contraceptive methods should be used during therapy

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**
Defer therapy on Day 1 of the cycle for 1 week if neutrophils <1.0 x 10^9/l or platelets <100 x 10^9/l
Omit Day 8 vinorelbine following symptomatic neutropenia or grade IV thrombocytopenia

Decrease vinorelbine dose to 75% if an episode of febrile neutropenia has occurred during previous cycles or if treatment has subsequently had to be delayed.

<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</td>
<td>and</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1.0-1.49</td>
<td>and</td>
<td>delay*</td>
<td>delay*</td>
</tr>
<tr>
<td>0.5-0.99</td>
<td>or</td>
<td>delay*</td>
<td>delay*/75% (day 8.)</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>or</td>
<td>delay*</td>
<td>delay*/omit** (day 8.)</td>
</tr>
</tbody>
</table>

* Delay entire cycle by 7 days on day 1.
**Omit vinorelbine dose completely if day 8 and consider dose reduction for next cycle.

**Vinorelbine Dose escalation after 1st cycle in Adjuvant/Induction setting**
If the first cycle is well tolerated, it is recommended to increase the dose of vinorelbine to 80mg/m²

Dose escalation of vinorelbine at cycle 2 is appropriate in the following settings:
Adjuvant setting, locally advanced where radical RT is planned, and when vinorelbine is used as a single agent.

Dose escalation should NOT occur in the palliative treatment of advanced disease unless vinorelbine is used as monotherapy.

When relevant, dose escalation should take place at cycle 2 only if:
- no grade 4 neutropenia (<0.5 x 10^9/l) at day 8.
- no febrile neutropenia

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<table>
<thead>
<tr>
<th>Reason for Update: Vinorelbine available strengths</th>
<th>Approved by Consultant: J.Spicer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version: 1.1</td>
<td>Supersedes: All other versions  Date: 01/08/08</td>
</tr>
<tr>
<td>Prepared by: SEestila April08, update Jan10</td>
<td>Checked by (Network Pharmacist): J.Turner</td>
</tr>
<tr>
<td>Approved by SELCN DTAC Chair: Nic Ketley 2008</td>
<td>Date: 01/2010</td>
</tr>
</tbody>
</table>
Vinorelbine Dose de-escalation from 2nd cycle onwards in Adjuvant/Induction setting
If grade 4 neutropenia (<0.5 x 10^9/l) occurs during cycles with 80mg/m^2 dose, delay treatment until recovery, then reduce to 60mg/m^2.

It is possible to re-escalate the dose after further 3 administrations with lower dose if well tolerated. Follow monitoring in following cycles as detailed above.

Renal Impairment
Vinorelbine: Dosage adjustment not required
Carboplatin: Contra-indicated if GFR < 20ml/min

Hepatic Impairment
If hepatic insufficiency is due to metastatic involvement, the 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 monitored.

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

<table>
<thead>
<tr>
<th>AST/ALT</th>
<th>Bilirubin</th>
<th>Vinorelbine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 x ULN</td>
<td>&lt;1.5 x ULN</td>
<td>Give 100%</td>
</tr>
<tr>
<td>5.1-20 x ULN</td>
<td>1.5-3 x ULN</td>
<td>Postpone and reassess in 1 week*/ 25-50% dose</td>
</tr>
<tr>
<td>&gt;20 x ULN</td>
<td>&gt;3 x ULN</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

*If liver toxicity persists for more than 3 weeks, discontinue treatment
*If day 8 vinorelbine, omit and dose reduce to next cycle

Dose modifications for other toxicities as appropriate

Neurological toxicity
For Grade 1 neurological toxicity, continue with 100% doses
For Grade 2 neurological toxicity, give 50% dose carboplatin, 100% vinorelbine
For Grade 3 or 4 neurological toxicity, discontinue treatment

Other toxicities (for neurotoxicity see above)

Grade 3 mucositis: give 100% carboplatin, 75% of vinorelbine
Grade 4 mucositis: give 75% carboplatin, 50% vinorelbine
Any other grade 3 toxicities, or any diarrhoea requiring hospitalisation: give 75% of previous doses
Any other grade 4 toxicities: Give 50% of previous doses, omit if day 8.
Grade 3 oesophagitis with radiotherapy: delay chemotherapy for 1 week, Continue radiotherapy if possible
Omit Vinorelbine in event of Grade 3 or 4 constipation and consider substituting with Carboplatin Gemcitabine regimen.

Drug interactions:
- Aprepitant: increased vinorelbine plasma levels
- Itraconazole: increased risk of neurotoxicity
- Posaconazole, voriconazole: increased vinorelbine plasma levels
- Omeprazole and fluoxetine may inhibit vinorelbine metabolism
- Phenytoin, carbamazepine: carboplatin decreases efficiency
- Nephrotoxic drugs (with carboplatin):
  - Aminoglycoside antibiotics: increased risk of ototoxicity (with carboplatin)
- Aluminium-containing equipment should not be used during preparation and administration of carboplatin

References:
- [www.medicines.org.uk](http://www.medicines.org.uk), accessed April 08
- SELCN Lung Diagnostic & Treatment Guidelines, July 06
- MAGE3-AS15-NSC-001 Trial protocol. Version Nov 06
- Vinorelbine PM0259CA224J1 Trial protocol. Version Nov 05
- CCO Formulary: VINOCARB. Revised Jan08
- Micromedex review, accessed April 08

The following table gives the **Vinorelbine** dose required for appropriate ranges of body surface area (BSA)

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Dose (mg)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.95 to 1.04</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>1.05 to 1.14</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>1.15 to 1.24</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>1.25 to 1.34</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>1.35 to 1.44</td>
<td>80</td>
<td>110</td>
</tr>
<tr>
<td>1.45 to 1.54</td>
<td>90</td>
<td>120</td>
</tr>
<tr>
<td>1.55 to 1.64</td>
<td>100</td>
<td>130</td>
</tr>
<tr>
<td>1.65 to 1.74</td>
<td>100</td>
<td>140</td>
</tr>
<tr>
<td>1.75 to 1.84</td>
<td>110</td>
<td>140</td>
</tr>
<tr>
<td>1.85 to 1.94</td>
<td>110</td>
<td>150</td>
</tr>
<tr>
<td>≥ 1.95</td>
<td>120</td>
<td>160</td>
</tr>
</tbody>
</table>

**Even for patients with BSA ≥ 2 m² the total Vinorelbine dose should never exceed 160mg per dose**