REGIMEN TITLE: Cisplatin Vinorelbine (Oral) therapy +/- radiotherapy

Indication: First line in Radical/ Induction, Adjuvant and Advanced & Palliative treatment of Non-small cell lung cancer patients
Eligible for patients able to tolerate and comply with oral dosage forms.

Regimen details:
Cisplatin 75mg/m² IV D1
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. Dose escalation to 80mg/m² does not take place when therapy is given with concomitant radiotherapy).

Note- when combined with radiotherapy, vinorelbine dose is reduced to 50-75% dose, depending on clinical oncologist’s recommendations.
2 or 3 cycles of radiotherapy may be given concomitantly with chemotherapy cycles.
Radiotherapy is dosed as 64Gy in 32 fractions.

See Appendix1. for vinorelbine dosing table according BSA

Administration:
Furosemide 40mg PO stat
Cisplatin:
1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO4 IV over 60 minutes
Cisplatin in 1 litre 0.9% Sodium Chloride IV over 2 hours
1 litre 0.9% Sodium Chloride + 40 mmol KCl + 1g MgSO4 IV over 2 hours
Then either 500ml Sodium Chloride 0.9% IV over 60 minutes or 500ml drinking water
*Follow guidance protocol for Hydration schedules & fluid balance monitoring for outpatient cisplatin regimens

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 cisplatin administration.

Frequency:
3 weekly cycle - Day 1. and Day 8.
Induction/ Adjuvant Total of 4 cycles
2-3 cycles may be given concomitantly with radiotherapy (note dose reductions as above)
Advanced/ palliative Total of 4-6 cycles

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

Extravasation: Cisplatin- non vesicant
Vinorelbine PO – not applicable
Regular investigations:
- FBC D1 and D8
- LFTs D1
- U&Es D1
- Mg and Ca D1
  (EDTA Prior to 1st cycle)
- Audiogram Prior to 1st cycle when clinically indicated
- Baseline CT

Clinical toxicity assessments (including neuropathy & local toxicity)

Comments: 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. Monitor trends in serum creatinine between treatments: if >25% from baseline value re-calculate GFR using the Cockcroft & Gault equation.

Encourage oral hydration during treatment; for instance drink a glass of water every hour during treatment, and at least a further 2 litres over the 24 hours following treatment. Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. For low urine output consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 kg, or symptoms of fluid overload.

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

Anaphylactic-like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of cisplatin administration. Adrenaline, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms

Dose Modifications

Haematological Toxicity
(see table next page)
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.
Neutrophils x 10^9/l  Platelets x 10^9/l  Cisplatin Dose  Vinorelbine dose  

<table>
<thead>
<tr>
<th>Neutrophils x 10^9/l</th>
<th>Platelets x 10^9/l</th>
<th>Cisplatin Dose</th>
<th>Vinorelbine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5</td>
<td>&gt;100</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1.0-1.49</td>
<td>&gt;100</td>
<td>delay*</td>
<td>delay*/100% (day 8.)</td>
</tr>
<tr>
<td>0.5-0.99</td>
<td>50-99</td>
<td>delay*</td>
<td>delay*/75% (day 8.)</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>&lt;50</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 check prior to next cycle.  
**Omit vinorelbine dose completely if day 8 and consider dose reduction for next cycle.

**Vinorelbine Dose escalation after 1st cycle in Adjuvant/Induction setting (not for RT patients)**
If the first cycle is well tolerated, it is recommended to increase the dose of vinorelbine to 80mg/m^2

Dose escalation of vinorelbine at cycle 2 is appropriate in the following settings:
Adjuvant/induction setting, 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, or for patients who are having concomitant chemotherapy regimen.

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

**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

**Cisplatin**

<table>
<thead>
<tr>
<th>CrCl (C&amp;G)(ml/min)</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>give 100%</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>carboplatin suggested</td>
</tr>
</tbody>
</table>

Cisplatin-induced nephrotoxicity is dose-related and cumulative. It manifests early by elevations in blood urea, creatinine, and wasting of potassium and magnesium. Renal function, fluid and electrolyte balance must return to normal prior to subsequent doses. Renal toxicity may be irreversible and is more prolonged and severe with repeated courses. Avoid concomitant use of other nephotoxic drugs (see ‘Drug interactions’).
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 followed up.

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
Grade 2 neurotoxicity - 50% dose of cisplatin, 100% vinorelbine
For Grade 3 or 4 neurotoxicity, treatment should be discontinued.

Neuro-hearing toxicity

<table>
<thead>
<tr>
<th>NCI CTC grade</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>no dose modification</td>
</tr>
<tr>
<td>2</td>
<td>50% reduced dose for further administrations</td>
</tr>
<tr>
<td>3-4</td>
<td>discontinue</td>
</tr>
</tbody>
</table>

Other toxicities (for neurotoxicity see above)

Grade 3 mucositis
Grade 4 mucositis
Any other grade 3 toxicities,
or any diarrhoea requiring hospitalisation
Any other grade 4 toxicities
Grade 3 oesophagitis with radiotherapy

Doses of cisplatin and vinorelbine

give 100% cisplatin, 75% of vinorelbine

give 75% cisplatin, 50% vinorelbine

give 75% of previous doses

Give 50% of previous doses, omit if day 8.
delay chemotherapy for 1 week, omit vinorelbine
Continue radiotherapy if possible

Omit vinorelbine in event of grade 3 or 4 constipation and consider substituting with cisplatin 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 – cisplatin decreases efficiency
Nephrotoxic drugs (with cisplatin)
Aminoglycoside antibiotics-increased risk of ototoxicity (with cisplatin)
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**