Vinorelbine 30 (Day 1,8,15) and CISplatin 80 (Day1) Therapy- 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Adjuvant treatment of patients with completely resected stage IB, II or IIIA non small cell lung cancer (NSCLC)	C34	00339a	Hospital
Treatment of locally advanced recurrent or metastatic NSCLC	C34	00339b	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

CISplatin is administered on day 1 and vinorelbine weekly on day 1, 8 and 15 of a 21 day cycle for 4 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,8 and 15	[a]Vinorelbine	30mg/m^2	IV infusion	50ml 0.9% sodium chloride over 15 min. Then flush the line with 250ml 0.9% sodium chloride prior to removing/capping IV access	Every 21 days for 4 cycles
2	1	[b]CISplatin	80mg/m^2	IV infusion	1000ml NaCl 0.9% over 2 hours (Pre and Post hydration therapy required)[b]	Every 21 days for 4 cycles

[a]Vinorelbine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here.

[b]**Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

- Administer 1000ml NaCl 0.9% over 1 hour
- Administer CISplatin as described above

Post hydration:

- Administer 1000ml NaCl 0.9% with 10mmol magnesium sulphate ($MgSO_4$) and 20mmol potassium chloride (KCl) over 2 hours

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (3,4).

ELIGIBILITY:

- Indications as above
- ECOG 0-1

EXCLUSIONS:

- Hypersensitivity to vinorelbine or other vinca alkaloids, CISplatin or any of the excipients
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- Pre existing neuropathies ≥ grade 2
- Pregnancy
- Lactation

USE with CAUTION:

- Neutrophil count < 1.5 x 10^9/L or severe infection; current or recent (within 2 weeks)
- Platelet count < 100 x 10^9/L

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, Renal and liver profile
- Audiometry and creatinine clearance as clinically indicated
- Assessment of peripheral neuropathy

Regular tests:

- FBC weekly
- Renal and liver profile prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Dose modification for haematological toxicity for vinorelbine on Day 1

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1.5	and	≥100	100% Dose
1-1.49	or	75-99	75%
< 1	or	< 75	Delay one week and repeat FBC[1,2]
[1]Delay entire cycle			
[2]If day 1 delayed with day 15 of preceding cycle having been delivered, omit vinorelbine on day 15 of upcoming and all subsequent cycles			
For vinorelbine on days 8 and 15			
≥1.5	and	≥100	100% Dose
1-1.49	or	75-99	75%
<1	or	<75	[3]Omit
[3]If ANC < 1 and/or platelets < 100 on day 15, omit vinorelbine on day 15 of all subsequent cycles			

Renal and Hepatic Impairment:

Table 2: Recommended dose modification of CISplatin and vinorelbine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment		
	Cr Cl (ml/min)	Dose	No dose reductions necessary		
CISplatin	>60	100%			
	45-59	75%			
	<45	Consider CARBOplatin-Clinical decision			
Vinorelbine	No dose reduction necessary		AST/ALT	Bilirubin	Dose
			>5 x ULN	> 2 x ULN	Reduce dose by 1/3
			ULN= Upper Limit of Normal		

Non-haematological toxicity:

Table 3: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Peripheral neuropathy Grade 2 Grade 3	 Withhold treatment until recovery to grade 1 then reduce the dose to 75% of the original dose. Discontinue treatment
Grade 3 constipation	After appropriate management of symptoms (See supportive care) may consider reducing the dose of vinorelbine to 75% of the original dose.
Other toxicities ≥Grade 3	 Defer therapy for 1 week until resolved to ≤ grade 1. Discuss with consultant if >1 week delay.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin High **(Refer to local policy)**
Vinorelbine Minimal **(Refer to local policy).**

PREMEDICATIONS:

Pre and Post Hydration therapy required for CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE:

- Mouth care **(Refer to local policy)**
- Prophylactic regimen against vinorelbine-induced constipation is recommended.
- Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Cardiac toxicity**: Special care should be taken when prescribing for patients with history of ischemic heart disease.
- **Extravasation:** Vinorelbine causes pain and tissue necrosis if extravasated **(Refer to local guidelines).**
- **Neutropenia:** The dose limiting adverse reaction of vinorelbine is mainly neutropenia. This effect is non-cumulative, having its nadir between 7 and 14 days after the administration and is rapidly reversible within 5 to 7 days. Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Constipation:** Constipation with vinorelbine should at a grade 1-2 be managed with dietary interventions or laxatives
- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.

DRUG INTERACTIONS:

- Risk of drug interactions causing increased concentrations of vinorelbine with CYP3A inhibitors.
- Risk of drug interactions causing decreased concentrations of vinorelbine with CYP3A inducers.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Current drug interaction databases should be consulted for more information

REFERENCES:

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Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	11/12/2017	Updated title, applied new NCCP regimen template, updated CISplatin hydration recommendations and dosing in renal and hepatic impairment	Prof Maccon Keane
3	15/05/2019	Amended administration table for vinorelbine.	Prof Maccon Keane
4	28/4/2021	Updated CISplatin hydration protocol with regard to KCl concentration	Prof Maccon Keane
5	24/06/2021	Updated CISplatin hydration protocol	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.