Vinorelbine and CISplatin Therapy- 28 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	00343a	Hospital
Treatment of locally advanced recurrent or metastatic NSCLC	C34	00343b	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 day 8 and vinorelbine weekly on day 1, 8, 15 and 22 of a 28 day cycle for 4 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the Systemic Anti-Cancer Therapy (SACT) is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,8, 15 and 22	[a]Vinorelbine	25mg/m^2	IV infusion	50ml 0.9% NaCl over 15min. Then flush the line with 250ml 0.9% NaCl prior to removing/capping IV access	Every 28 days for 4 cycles
2	1 and 8	[b]CISplatin	50mg/m^2	IV infusion	1000ml NaCl 0.9% over 60 mins	Every 28 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.
https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf

[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 60 mins
- Administer CISplatin as described above

Post hydration:
Administer 10mmol magnesium sulphate (MgSO4) and 20mmol potassium chloride (KCl) in 1000 ml 0.9% NaCl 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 .

ELIGIBILITY:

- Indications as above
- Life expectancy > 3 months
- 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: Recommended dose modification of vinorelbine based on neutrophil counts

ANC (x10^9/L)	Dose*
≥1.5	100% starting dose
1-1.49	50% starting dose
< 1	Delay one week and repeat FBC. If 3 consecutive weekly doses are held because neutrophil count is <1.0 x 10^9/L, discontinue vinorelbine
***Dose adjustment**: For patients who during treatment, have experienced fever or sepsis while neutrophils were <1.5 x 10^9/L or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of vinorelbine should be given as follows	
ANC (x10^9/L)	**Dose**
≥1.5	75% starting dose
1-1.49	37.5% starting dose
< 1	Delay until count recovery and follow the above dosing guidelines

Renal and Hepatic Impairment:

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

Drug	Renal Impairment		Hepatic Impairment		
CISplatin	**Cr Cl (ml/min**	**Dose**	No dose reductions necessary		
	>60	100%			
	45-59	75%			
	<45	Delay			
vinorelbine	No dose reduction necessary		**AST/ALT**	**Bilirubin**	**Dose**
			>5 x ULN	> 2 x ULN	Reduce dose by 33%
			ULN= Upper Limit of Normal		

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)**

- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.

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)**
- Patients should be counseled on the risk of constipation associated with the use of vinca alkaloids. Dietary interventions or prophylactic laxatives may be required.
- 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.
- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.
- 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	20/06/2016		Prof Maccon Keane
2	20/06/2018	Updated with new NCCP regimen template. Update of treatment table to: • Standardise fluid and infusion times. • Amend CISplatin hydration recommendations Update to dosing in hepatic and renal impairment	Prof Maccon Keane

		Emetogenic potential updated	
3	21/08/2019	Updated recommended dose modification of vinorelbine based on neutrophil counts	Prof Maccon Keane
4	10/06/2020	Reviewed.	Prof Maccon Keane
5	24/06/20201	Updated CISplatin hydration protocol	Prof Maccon Keane
6	15/05/2023	Updated infusion time for CISplatin. Updated hydration instructions. Updated emetogenic potential and drug interations section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.