CARBOplatin and vinORELbine Therapy-21 Day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of locally advanced, recurrent or metastatic non-small cell lung cancer (NSCLC) in patients not suitable for treatment with CISplatin	C34	00614a	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.

CARBOplatin is administered on day 1 and vinORELbine is administered on days 1 and 8 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	[a]vinORELbine	25mg/m^2	IV infusion	50ml 0.9% NaCl over 15 mins. Then flush the line with 250ml 0.9% NaCl prior to removing/capping IV access.	Every 21 days for 4 cycles
2	1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 30 min.	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. https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- Measured GFR (e.g. nuclear renogram) is preferred whenever feasible. Estimation of GFR (eGFR) can be done by using the Wright formula or using the Cockroft and Gault formula to measure creatinine clearance
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.

- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight for Cockroft and Gault may be considered (2).

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay*.

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (µmol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (µmol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\textbf{GFR (ml/min)} = \frac{\textbf{S} \times \textbf{(140 - age in years)} \times \textbf{wt (kg)}}{\textbf{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate hematologic, hepatic and renal function

EXCLUSIONS:

- Hypersensitivity to vinORELbine or other vinca alkaloids, cARBOplatin or any of the excipients
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Peripheral neuropathy assessment

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Peripheral neuropathy assessment 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 of CARBOplatin and vinORELbine in haematological toxicity

ANC (x 10^9/L)	
0.5 to < 1.0	Delay treatment until recovery
< 0.5	Delay treatment until recovery and reduce vinORELbine and CARBOplatin by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and reduce vinORELbine and CARBOplatin by 25% for subsequent cycles
Prolonged recovery greater than two weeks delay, or 3rd delay for myelosupression	Delay treatment until recovery and reduce vinORELbine and CARBOplatin by 50% for subsequent cycles or cease
Platelets (x 10^9/L)	
50 to <100	Delay treatment until recovery
<50	Delay treatment until recovery and reduce vinORELbine and CARBOplatin by 25% for subsequent cycles

Renal and Hepatic Impairment:

Table 2: Dose modification of CARBOplatin and vinORELbine in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment		
CARBOplatin	See note below*	No dose modification required		
vinORELbine	No dose modification required	**AST/ALT**	**Bilirubin**	**Dose**
		>5 x ULN	> 2 x ULN	Reduce dose by 33%
		ULN= Upper Limit of Normal		

***Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20ml/min, CARBOplatin should not be administered at all.
- If Cockroft & Gault or Wright formulae are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockroft & Gault or Wright formulae taking care this does result in a dose reduction.

Management of adverse events:

Table 3: Dose Modifications for Adverse Events

Adverse reactions	Recommended dose modification
Peripheral neuropathy	
Grade 2 which is present at start of next cycle	Reduce vinorelbine by 25%; if persistent, reduce vinorelbine by 50%
Grade 3 or grade 4	Omit vinorelbine
Mucositis and stomatitis	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce dose for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce carboplatin and vinorelbine by 25% 3rd occurrence: Reduce carboplatin and vinorelbine by 50% 4th occurrence: Omit carboplatin and vinorelbine
Grade 3 or grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Reduce carboplatin and vinorelbine by 50% 2nd occurrence: Omit carboplatin and vinorelbine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CARBOplatin: High (**Refer to local policy).**
vinORELbine: Minimal (**Refer to local policy).**

PREMEDICATIONS:

Not usually required

OTHER SUPPORTIVE CARE:

- 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.

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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 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 should at a grade 1-2 be managed with dietary interventions or laxatives. Laxatives and careful monitoring of bowel mobility are recommended in patients receiving concomitant morphine or opioid analgesics.
- **Fructose intolerance:** Due to sorbitol content, patients with rare hereditary problems with fructose intolerance should not take the capsules.
- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However, allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years

DRUG INTERACTIONS:

- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary, monitor renal function closely.
- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary, perform regular audiometric testing.
- Risk of drug interactions causing increased concentrations of vinorelbine with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of vinorelbine with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CARBOplatin - L01XA02
VinORELlbine - L01BC05

REFERENCES:

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Version	Date	Amendment	Approved By
1	2/12/2020		Prof Maccon Keane

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