# 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 |

**If the reimbursement status is not defined [1], the indication has yet to be assessed through the formal HSE reimbursement process.*

## 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 120mins (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.

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

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins
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).

## ELIGIBILTY:

- 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: For vinorelbine on Day 1**

| ANC (x$10^9$/L) | | Platelets (x$10^9$/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: Reccommended dose modification of CISplatin and gemcitabine 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** | | |

**Table 3: Dose modification schedule based on adverse events**

| Adverse reactions | Recommended dose modification |
|---|---|
| **Peripheral neuropathy**<br>Grade 2<br><br>Grade 3 | <br>Withhold treatment until recovery to grade 1 then reduce the dose to 75% of the original dose.<br><br>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**<br>≥Grade 3 | <br>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

## ATC CODE:

| | |
|---|---|
| Vinorelbine | L01BC05 |
| CISplatin | L01XA01 |

## REFERENCES:


1. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004; 350: 351-360.
2. BCCA Protocol Summary for Adjuvant CISplatin and Vinorelbine Following Resection of Non-Small Cell Lung Cancer LUAJNP Revised July 2018
3. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
4. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017 https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
5. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf

6. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
7. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed May 2019 . Available at https://www.hpra.ie/img/uploaded/swedocuments/Final%20approved%20SPC%20PA0822.199.001.pdf
8. Navelbine ®Summary of Product Characteristics Accessed May 2019 Available at https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1287-001-005_06022017150040.pdf

| 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 |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/