Regimen Monograph

A - Regimen Name

CISPVINO(RT) Regimen

CISplatin-Vinorelbine

Disease Site	Lung - Non-Small Cell
Intent	Neoadjuvant Curative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Chemo-radiotherapy for patients with unresected, clinical or pathological stage III NSCLC with good performance status (ECOG ≤ 1) and minimal weight loss (<5% in the past 3 months).

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B - Drug Regimen

Chemoradiotherapy - Chemotherapy concurrent with Radiotherapy

vinorelbine[1]	15 mg /m²	IV	Days 1 and 8

[1] Note: Dosage of vinorelbine reduced with concurrent radiation as full doses are intolerable.

CISplatin	80 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS DURING RADIOTHERAPY

Notes: There is limited evidence for induction chemotherapy prior to chemo-radiation and it is not recommended. There is also limited evidence for 'consolidation' chemotherapy after the completion of chemo-radiation; if used, 2 to 3 cycles could be considered.

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (Cisplatin)
Minimal (Vinorelbine Only days)

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Summary

Standard regimens for Cisplatin premedication and hydration should be followed. Refer to Cisplatin monograph

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are based on Vokes (2002) and the Drug Monographs for each drug.

Dosage with toxicity

Hematologic Toxicities:

Granulocyte counts (x 10^9/L) on treatment day	Platelet Counts (x 10^9/L) on treatment day	Dose[1]
1 to 1.4	50 to 75	Cisplatin and Vinorelbine ↓ by 50%
<1	<50	Hold Cisplatin and Vinorelbine doses

[1] Vokes et al

Non-hematologic toxicities

Worst Toxicity / Counts (x 10^9/L) Experienced	Cisplatin (% previous dose)*	Vinorelbine (% previous dose)*
Grade 2 neurotoxicity	↓ to 50%[1]	↓ to 50%[1]
Grade 3 neurotoxicity	Discontinue	Discontinue
Grade 3 or 4 radiotherapy related toxicities (e.g. diarrhea, stomatitis, dermatitis, esophagitis)	No change[1]	Hold, then ↓ 50%[1]
↑ creatinine (1.5 to 1.99 x ULN)	↓ by 50%	No change
↑ creatinine (≥ 2x ULN)	Hold until recovered to ≤ 2 x ULN and ↓ as indicated	No change
Other related grade 3 non-hematologic/organ	Hold; reduce by 25%	Hold; reduce by 25%
Other related grade 4 non-hematologic/organ	Consider discontinuing	Consider discontinuing

*Do not re-treat until toxicities have recovered to ≤ grade 2

[1] Vokes 2002

Hepatic Impairment

Suggested adjustments for increases in total bilirubin:

Total Bilirubin (µmol/L)	Cisplatin (% usual dose)	Vinorelbine (% usual dose)
< 2 x ULN	No adjustment needed	100%
2 to 3 x ULN		50%
> 3 x ULN		25%

Renal Impairment

See specific protocol. In general, renal function should have normalized before patients are re-treated. If continued treatment is considered to be mandatory, the following dose modifications could be considered at the physician's discretion (Kintzel 1995).

Creatinine clearance	Cisplatin (% usual dose)	Vinorelbine (% usual dose)
46 to 60	75%	No adjustment needed
30 to 45	50%	
<30	Discontinue	

Dosage in the Elderly:

Geriatric patients may be at higher risk of developing nephrotoxicity, ototoxicity/neurotoxicity or hematologic adverse effects with cisplatin

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F - Adverse Effects

Refer to vinorelbine, CISplatin drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± infection / bleeding (may be severe) • Nausea and vomiting • Anorexia • Fatigue • Stomatitis, diarrhea • Nephrotoxicity (may be severe) • Electrolyte abnormalities • Neurotoxicity and ototoxicity (may be severe) • Constipation (may be severe) • Hyperuricemia • Reproductive risk • Esophagitis (may be severe) • Diarrhea • Pain • Local/infusion site toxicity • Alopecia	• Arterial thromboembolism • Venous thromboembolism • Arrhythmia • Hemolytic uremic syndrome • Secondary malignancies • Seizures • Hypersensitivity • Hemolysis • Optic neuritis • Pneumonitis and ARDS • SIADH • Vasculitis • Thrombotic microangiopathy

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G - Interactions

Refer to vinorelbine, CISplatin drug monograph(s) for additional details

- Avoid nephrotoxic and ototoxic drugs (i.e. aminogycosides) due to additive effects
- Concomitant use of renally excreted drugs (i.e. methotrexate) may decrease renal clearance and enhance toxicities of these drugs. Avoid use, if possible. If not possible, modify doses as necessary.
- Avoid strong CYP3A4 inhibitors (i.e. ketoconazole)

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H - Drug Administration and Special Precautions

Refer to vinorelbine, CISplatin drug monograph(s) for additional details

Drug Administration:

Cisplatin:

- Follow local hydration protocols to prevent/minimize nephrotoxicity
- Dilute in NS and administer IV over 30-60 minutes
- Blood pressure should be taken before and after chemotherapy.
- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.
- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

Vinorelbine:

FOR INTRAVENOUS USE ONLY.

Intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing this product should be labeled "WARNING – FOR INTRAVENOUS USE ONLY. FATAL if given intrathecally."

- Dilute in a 50mL minibag (D5W, NS) to a final concentration 0.5 - 2mg/mL; infuse over 6-10 minutes through free-flowing IV.
- Or may push (at final concentration of 1.5 – 3mg/mL) through sidearm of free-flowing IV (D5W, NS); inject over 6-10 minutes.
- Flushing the line before and after administration of vinorelbine may reduce injection site reactions and phlebitis risk.
- Refrigerate unopened vials (2-8°C); protect from light and do not freeze.

Contraindications:

- Known hypersensitivity to platinum containing compounds or vinca alkaloids
- Patients who have severe myelosuppression
- Pre-existing renal impairment and hearing impairment, unless the possible benefits of treatment outweigh the risks.

Other Warnings/Precautions:

- Patients with pre-existing neuropathy or prior treatment with other neurotoxic drugs may have increased potential for neurotoxicity

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

- CBC; Baseline and before each dose
- Liver function tests; Baseline and before each dose
- Renal function tests; Baseline and before each cisplatin dose
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium.; Baseline and before each cisplatin dose
- Audiogram; Baseline and as clinically indicated
- Clinical toxicity assessment for signs of neurotoxicity, local toxicity, bleeding, infection, nausea/vomiting, neurotoxicity, ototoxicity, hypersensitivity, thromboembolism, lung toxicity; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	Cisplatin-Vinorelbine: 4 hours; Vinorelbine only: 0.5 hours
Pharmacy Workload (average time per visit)	29.576 minutes
Nursing Workload (average time per visit)	41.667 minutes

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K - References

Cisplatin and vinorelbine drug monographs, Cancer Care Ontario.

Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Cancérologie

NPC 95-01 Study. J Clin Oncol 23:5910-5917.

Hirose T, Mizutani Y, Ohmori T, et al. The combination of cisplatin and vinorelbine with concurrent thoracic radiation therapy for locally advanced stage IIIA or IIIB non-small-cell lung cancer. Cancer Chemother Pharmacol. 2006 Sep: 58(3):361-7.

Vokes E, Herndon J, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B Study 9431. JCO; 20(20): 4191-4198 (2002).

Zatlouka P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer. 2004 Oct;46(1):87-98.

PEBC Advice Documents or Guidelines

- Treatment of Patients with Stage III (N2 or N3) Non-Small Cell Lung Cancer

June 2019 Added PEBC guideline link

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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