Regimen Monograph

A - Regimen Name

CRBP Regimen

CARBOplatin

Disease Site	Head and Neck
Intent	Palliative
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	Treatment of metastatic or recurrent squamous cell head and neck cancer

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B - Drug Regimen

CARBOplatin	AUC 5 to 6	IV	Day 1

Adjust Carboplatin dose to AUC target (using Calvert formula) as outlined in the "Other Notes" section.

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For up to 6 cycles unless disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)

Febrile Neutropenia Risk: Low

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Pre-medications (prophylaxis for infusion reactions):

- There is insufficient evidence that routine prophylaxis with pre-medications reduce infusion reaction (IR) rates.
- Corticosteroids and H1-receptor antagonists ± H2-receptor antagonists **may** reduce IR rates for some patients (e.g. gynecological patients with a PFI >12 months or a history of drug allergy who are receiving carboplatin starting from the 7th cycle) but no optimal pre-medication regimen has been established.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Below are suggested dose modifications.

Toxicity / Counts (x 10^9/L)	Dose Modification
ANC < 1.5 but ≥ 0.5 and/or	Hold#; may consider dose ↓

Platelets < 100 but ≥ 25	at restart
Febrile Neutropenia OR ANC < 0.5 for ≥ 5-7 days OR Platelets < 25	Hold# Restart by ↓ 25%
Grade 3 related organ / non-hematologic	Hold# Restart by ↓ 25%
Grade 4 related organ / non- hematologic	Discontinue

Do not retreat unless platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L and toxicities have recovered to ≤ grade 2.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

There is insufficient evidence that routine prophylaxis with extended infusion reduces IR rates.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• There is evidence that re-challenging with **cisplatin** after carboplatin reaction can be a viable option. • **However**: exact cross reactivity between platinum agents is not known, but can be as high as 25%. • Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge • May consider adding oral montelukast ± oral acetylsalicylic acid
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been

		affected. • Consider desensitization if therapy is necessary.

* Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist

Hepatic Impairment

No dose adjustment required.

Renal Impairment

Creatinine Clearance (ml/min)	Carboplatin (% previous dose)
20 - 50	Use Calvert formula*
< 20	Discontinue

*See "Other Notes" section

Dosage in the Elderly

Caution should be exercised and dose reduction considered as elderly patients may have reduced renal function, more severe myelosuppression and neuropathy.

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F - Adverse Effects

Refer to CARBOplatin drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or

			life-threatening
• Myelosuppression ± infection, bleeding (may be severe) • Nausea, vomiting	• Abnormal electrolyte(s) • Nephrotoxicity (may be severe)	• ↑ BUN • ↑ LFTs (transient) • Hearing impairement • Fatigue (may be severe)	• Arterial / Venous thromboembolism • Peripheral neuropathy • Hypersensitivity • Encephalopathy • Hemolytic anemia • Hemolytic uremic syndrome • Secondary malignancy • Veno-occlusive disease • Visual disturbances

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G - Interactions

Refer to CARBOplatin drug monograph(s) for additional details

- Monitor closely with other nephrotoxic drugs, including aminoglycosides

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H - Drug Administration and Special Precautions

Refer to CARBOplatin drug monograph(s) for additional details

Administration

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.
- There is insufficient evidence that routine prophylaxis with extended infusion reduces IR rates.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients who have a severe allergic reaction to this drug or other platinum-containing compounds
- Patients with pre-existing severe renal impairment
- Patients with severe myelosuppression or bleeding tumours

Other Warnings/ Precautions

- Patients with abnormal renal function or who are receiving concomitant nephrotoxic drugs.
- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age.
- Avoid live vaccines. Reduced immunogenicity may occur with the use of inactivated vaccines.

Pregnancy/ Lactation

- Carboplatin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose (general recommendation).

- Breastfeeding is not recommended.
- Fertility effects: Unknown

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Renal function tests (including electrolytes); baseline and before each cycle
- Clinical toxicity assessment for neurotoxicity, ototoxicity, hypersensitivity, bleeding, infection, nausea and vomiting; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Liver function tests; baseline and as clinically indicated
- INR for patients receiving warfarin; baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	0.5-1 hour
Pharmacy Workload (average time per visit)	22.220 minutes
Nursing Workload (average time per visit)	44.167 minutes

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K - References

Clavel M, Vermorken JB, Cognetti F, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in

recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1994;5(6):521-6.

Hong WK, Schaefer S, Issell B, et al. A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. Cancer 1983;52(2):206-10.

Jacobs C, Lyman G, Velez-García E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992;10(2):257-63.

PEBC Advice Documents or Guidelines

- The Management of Head and Neck Cancer in Ontario

November 2019 Updated Adverse Effects, Interactions, Administration and Special Precautions sections. Updated infusion reaction information in Premedication, Dose Modifications and Drug Administration and Special Precautions sections.

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L - Other Notes

Calvert Formula

DOSE (mg) = target AUC X (GFR + 25)

- AUC = product of serum concentration (mg/mL) and time (min)
- GFR (glomerular filtration rate) expressed as measured Creatinine Clearance or estimated from Serum Creatinine (by Cockcroft and Gault method or Jelliffe method)

(Calvert AH, Newell DR, Gumbrell LA, et al, Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol, 1989; 7: 1748-1756)

To avoid toxicity, FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a capped GFR estimate at 125 mL/min for patients with normal renal function:

Maximum Carboplatin Dose (mg) = target AUC (mg/mL per min) x (125 mL/min + 25)

For a target AUC = 6, the maximum dose is 6 x 150 = 900 mg

For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg

For a target AUC = 4, the maximum dose is 4 x 150 = 600 mg

(U.S. Food and Drug Administration, Center for Drug Evaluation and research. Carboplatin dosing. 10 October 2010)

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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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