Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

CRBPGEMC(W) Regimen

Gemcitabine-CARBOplatin

Disease Site	Breast
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	For the treatment of metastatic breast cancer.

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B - Drug Regimen

CARBOplatin	AUC 2	IV	Days 1, 8
gemcitabine	800 mg /m²	IV	Days 1, 8

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression, no evidence of further response, or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:
Also refer to CCO Antiemetic Summary

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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 have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Dose on Day 1 of Cycle:

Worst Toxicity in Previous Cycle			Gemcitabine	Carboplatin
Non-Hematologic (related organ)		**Hematologic (counts x 10^9/L)**	**% Full Dose[1]**	**% Full Dose[1]**
Grade 3	or	Febrile neutropenia, thrombocytopenic bleeding, ANC < 0.5 for > 5 days or < 0.1 for > 3 days, or platelets < 25	75%[2]	75%[3]
Grade 4			Consider discontinuing,	Consider discontinuing,

			or ↓ to 50-75%[4]	or ↓ to 50-75%[4]
Day 8 holds in > 1 cycle			75%	100%
Pneumonitis			Hold and investigate. If confirmed, discontinue	Hold and investigate. If confirmed, discontinue.
Hemolytic Uremic Syndrome (HUS), Capillary Leak Syndrome (CLS)			Discontinue	Consider Discontinue
Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)			Discontinue	Consider Discontinue

[1] do not retreat until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and toxicity ≤ grade 2.

[2] if toxicity recurs after gemcitabine dose reduction, omit day 8 gemcitabine.

[3] use Egorin formula if isolated thrombocytopenia.

[4] if the reduced dose is tolerated well, a re-increase to 75% may be considered for the following cycle

Dose on Day 8 of Cycle:

Toxicity on Day 8 of cycle					**Day 8 dose**	
Non-hematologic (related organ)		**Hematologic**			**Gemcitabine (% Full Dose)**	**Carboplatin (% Full Dose)**
		ANC (x 10^9/L)		**Platelets (x 10^9/L)**		
≤ grade 2	and	≥ 1.5	and	≥ 100	100%	100%
≤ grade 2	and	1.0-1.49	and/or	75-99	↓ to 50%	↓ to 50%
grade 3 or 4	and/or	< 1.0	and/or	< 75	Omit	Omit
Pneumonitis		-		-	Discontinue	Consider

HUS SJS TEN CLS						Discontinue

Hepatic Impairment

Bilirubin		AST/ALT	Gemcitabine (% previous dose)	Carboplatin (% previous dose)
1-2 x ULN	And/or	<2 x ULN	100%	100%
2-4 x ULN		2-5 x ULN	Caution	100%
> 4 x ULN		> 5 x ULN	Caution, consider ↓	Caution, consider ↓

Renal Impairment

CrCl (mL/min)	Gemcitabine (% previous dose)	Carboplatin (% previous dose)
> 60	100%	Use Calvert formula
40-60	100%	
20-40	Caution	
< 20	Consider discontinuing or ↓	Discontinue

Dosage in the Elderly

Caution should be exercised and dose reduction considered for carboplatin as elderly patients may have more severe myelosuppression and neuropathy.

Gemcitabine clearance is lower in the elderly but no dose adjustment necessary.

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F - Adverse Effects

Refer to gemcitabine, 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
• Elevated LFTs (may be severe) • Nausea or vomiting • Myelosuppression ± infection, bleeding (may be severe)	• Fatigue, flu-like symptoms • Nephrotoxicity, proteinuria • Rash (may be severe)	• Edema • Musculoskeletal pain • Neurotoxicity (ototoxicity) • Alopecia • Diarrhea • Abnormal Electrolytes	• Pneumonitis • Hemolytic-uremic syndrome • Secondary malignancies • Capillary leak syndrome • Arterial/venous thromboembolism • Arrhythmia • Cardiotoxicity • Hypersensitivity • Vasculitis • PRES

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G - Interactions

Refer to CARBOplatin, gemcitabine drug monograph(s) for additional details

- Caution concurrent use of nephrotoxic and ototoxic medications due to additive effects with carboplatin.
- Carboplatin may cause a decrease in phenytoin levels; monitor closely and increase phenytoin dose if necessary.
- Monitor INR closely with concurrent warfarin as both gemcitabine and carboplatin may increase INR and bleeding risk.

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H - Drug Administration and Special Precautions

Refer to CARBOplatin, gemcitabine drug monograph(s) for additional details

Administration:

Carboplatin:

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

Gemcitabine:

- May dilute reconstituted drug in normal saline for IV infusion, resulting in a minimum final concentration of at least 0.1 mg/mL.
- Infuse over 30 minutes through free-flowing IV. Infusion time beyond 60 minutes has been shown to increase toxicity.

Contraindications:

- Patients who have a hypersensitivity to these drugs or other platinum-containing compounds
- Patients with severe renal impairment, severe myelosuppression or bleeding tumours

Other Warnings/Precautions:

- Patients with abnormal renal function or who are receiving concomitant nephrotoxic drugs
- Patients with impaired hepatic function, including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis
- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Patients receiving concurrent radiation while receiving full dose gemcitabine should be closely monitored for reactions
- Potentially life-threatening esophagitis and pneumonitis, particularly in patients receiving large volumes of radiotherapy have been observed.

Pregnancy and Lactation:

- Carboplatinn and gemcitabine are 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 (for women of childbearing potential).
- Breastfeeding is not recommended.
- Fertility effects: Probable (gemcitabine)

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I - 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.

Recommended Clinical Monitoring

- CBC; baseline and before each treatment
- Liver function tests; baseline and before each cycle
- Renal function tests and electrolytes (including magnesium); baseline and before each cycle
- Clinical toxicity assessment (including flu-like symptoms, fatigue, rash, edema, GI, pulmonary, neurotoxicity, infection, bleeding, ototoxicity); at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- INR for patients receiving warfarin; Baseline and as clinically indicated
- Urinalysis; Baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	2 hours
Pharmacy Workload (average time per visit)	34.575 minutes
Nursing Workload (average time per visit)	49.167 minutes

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K - References

Carboplatin and gemcitabine drug monographs, Cancer Care Ontario.

Chan D, Yeo WL, Tiemsim Cordero M, et al. Phase II study of gemcitabine and carboplatin in metastatic breast cancers with prior exposure to anthracyclines and taxanes. Invest New Drugs. 2010 Dec;28(6):859-65.

Laessig D, Stemmler HJ, Vehling-Kaiser U, et al. Gemcitabine and carboplatin in intensively

pretreated patients with metastatic breast cancer. Oncology. 2007;73(5-6):407-14.

Maisano R, Zavettieri M, Azzarello D, et al. Carboplatin and gemcitabine combination in metastatic triple-negative anthracycline- and taxane-pretreated breast cancer patients: a phase II study. J Chemother. 2011 Feb;23(1):40-3.

Nagourney RA, Flam M, Link J, et al. Carboplatin plus gemcitabine repeating doublet therapy in recurrent breast cancer. Clinical Breast Canacer. 2008;8(5): 432-5.

Yardley DA, Burris HA 3rd, Simons L, et al. A phase II trial of gemcitabine/carboplatin with or without trastuzumab in the first-line treatment of patients with metastatic breast cancer. Clin Breast Cancer. 2008 Oct;8(5):425-31.

December 2018 Updated regimen name to reflect the weekly schedule.

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L - Other Notes

Carboplatin dosing by BSA is not recommended as it does not take into account of the patient's renal function and/or desired platelet nadir, which may result in overdosing (i.e. patients with poor renal function) or underdosing (i.e. with above average renal function). Several methods have been proposed for calculating carboplatin doses, considering the area under the curve (AUC) and its subsequent hematologic toxicity, and also the direct relationship between glomerular filtration and carboplatin clearance.

Calvert Formula: (Most commonly used method)

Dose (**mg**) = Target AUC (mg/mL per min) x [CrCl† (mL/min) + 25]
(See "References - Appendix" section)

†Note: Older laboratory methods of measuring creatinine overestimated low levels of creatinine. Serum creatinine measured by the Isotope Diluted Mass Spectrometry (IDMS) method accurately measures creatinine, producing potentially lower levels than would have been reported with older methods; thus the lower limits of normal are significantly lower than the limits in the past. Using the IDMS method, if the creatinine levels are low, the calculated creatinine clearance (CrCl) and the estimated GFR may be substantially higher than the normal GFR when formally measured using radioisotopic methods. The Calvert formula was developed using the older methodology for creatinine measurement, and using it uncapped may result in certain patients with low serum creatinine levels appearing to have a very high GFR, and thus receiving very high and inappropriate carboplatin doses with resulting toxicity.

To avoid toxicity, FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a GFR estimate that is capped 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)

(See FDA communication on carboplatin dosing)

Egorin Formula: Takes into account of BSA, creatinine clearance, desired platelet nadir and pretreatment platelet count. (See "References - Appendix" section)

Chatelut Formula:

Dose (**mg**) = Target AUC (mg/mL per min) x Carboplatin clearance (mL/min)

(See "References - Appendix" section)
The Chatelut formula should not be used in pediatric or hemodialysis patients.

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M - Disclaimer

Regimen Abstracts

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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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