Regimen Monograph

A - Regimen Name

CRBPGEMC Regimen

Gemcitabine-CARBOplatin

Disease Site

Genitourinary
Bladder / Urothelial

Intent

Neoadjuvant
Adjuvant
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.

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B - Drug Regimen

gemcitabine	1000 mg /m²	IV	Days 1 and 8
CARBOplatin	AUC 5 to 6	IV	Day 1

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

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Neoadjuvant / Adjuvant: For a 3 to 4 cycles unless disease progression or unacceptable toxicity occurs

Palliative: For up to 8 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5) (D1)
Low (D8)

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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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**	**% Full Dose***	**% Full Dose***
Grade 3	or	Febrile neutropenia, thrombocytopenic bleeding	75%	75%#
Grade 4			Consider discontinuing, or ↓ to 75%	Consider discontinuing, or ↓ to 75%
Day 8 holds in > 1 cycle			75%	100%
Pneumonitis, Hemolytic Uremic Syndrome (HUS), Capillary Leak Syndrome (CLS), Posterior reversible encephalopathy syndrome (PRES)			Discontinue	Discontinue
Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)			Discontinue	Discontinue
* Do not retreat until AGC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and toxicity ≤ grade 2. # use Egorin formula if isolated thrombocytopenia				

Dose on Day 8 of Cycle:

Toxicity on Day 8 of cycle					
Non-hematologic (related organ)		**Hematologic**			**Gemcitabine (% Full Dose)**
		AGC (x 10^6/L)		**Platelets (x 10^6/L)**	
≤ grade 2	and	> 1000	and	> 100,000	100%
≤ grade 2	and	500-1000	or	50,000-100,000	Consider Omit, or ↓ to 75%
Grade 3 or 4	or	< 500	or	< 50,000	Omit, ↓ to 75% at restart (if applicable) for non-hematologic toxicity
• Pneumonitis • HUS • SJS • TEN • CLS • PRES		-		-	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

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F - Adverse Effects

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

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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

- Clinical toxicity assessment (including flu-like symptoms, fatigue, rash, edema, GI, pulmonary, neurotoxicity, infection, bleeding, ototoxicity).
- CBC before each cycle and on day 8.
- Baseline and regular liver function tests
- Baseline and regular renal function tests and electrolytes (including magnesium)
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	Day 1: 2 hours; Day 8: 45 minutes
Pharmacy Workload (average time per visit)	28.715 minutes
Nursing Workload (average time per visit)	42.917 minutes

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K - References

Carboplatin, gemcitabine drug monographs, Cancer Care Ontario.

Neoadjuvant / adjuvant:

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48(2):202-5.

Booth CM, Siemens DR, Li G, et al. Perioperative chemotherapy for muscle-invasive bladder cancer: A population-based outcomes study. Cancer 2014;120(11):1630-8.

Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol 2012;23(3):695-700.

Dash A, Pettus JA 4th, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008;113(9):2471-7.

Yeshchina O, Badalato GM, Wosnitzer MS, et al. Relative efficacy of perioperative gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management of locally advanced urothelial carcinoma of the bladder. Urology 2012 Feb;79(2):384-90.

Palliative:

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30(2):191-9.

Dogliotti L, Cartenì G, Siena S, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol. 2007;52(1):134-41.

von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, Phase III Study. J Clin Oncol 2000;18(17):3068-77.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Metastatic Urothelial Cancer: Endorsement of a Portion of the European Association of Urology Guideline on Muscle-Invasive and Metastatic Bladder Cancer

September 2022 added PEBC guideline

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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)

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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