Regimen Monograph

A - Regimen Name

CISPGEMC Regimen

Gemcitabine-CISplatin

Disease Site	Genitourinary Bladder / Urothelial
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 advanced or metastatic urothelial cancer

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B - Drug Regimen

Standard schedule:

gemcitabine	1000 mg /m²	IV	Days 1, 8 and 15
CISplatin	70 mg /m²	IV	Day 1

Alternative Schedule:

gemcitabine	1000-1250 mg /m²	IV	Days 1 and 8
CISplatin	70 mg /m²	IV	Day 1

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C - Cycle Frequency

Standard Schedule: REPEAT EVERY 28 DAYS

Alternative Schedule: REPEAT EVERY 21 DAYS

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

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (D1)
Low (D8, 15)

Other Supportive Care:

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

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.

Dosage with toxicity

Dose on Day 1 of Cycle:

Worst Toxicity in Previous Cycle			Gemcitabine	Cisplatin
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 or 15 holds in > 1 cycle			75%	100%
• Pneumonitis • Hemolytic Uremic Syndrome (HUS) • Stevens-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • Capillary Leak Syndrome (CLS)			Discontinue	Discontinue

* Do not restart until ANC ≥ 1500x 10^6/L, platelets ≥ 100,000 x 10^6/L and non-hematologic toxicity ≤ grade 2.

Dose on Day 8 and 15 (if applicable) of Cycle:

Toxicity on Day 8 or 15 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		-		-	Discontinue

*If day 15 is omitted, may use q21 day cycle.

Hepatic Impairment

Bilirubin		**AST/ALT**	**Gemcitabine (% previous dose)**	**Cisplatin (% 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

Creatinine Clearance (mL/min)	**Gemcitabine (% previous dose)**	**Cisplatin (% previous dose)**
> 60	100%	100%
>45-60	Caution	75%
30-45	Caution	50%
< 30	Consider discontinuing or ↓	Discontinue

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F - Adverse Effects

Refer to gemcitabine, 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) • Fatigue, flu-like symptoms, musculoskeletal pain • Edema • Nausea and vomiting • Elevated LFTs (may be severe) • Neurotoxicity and ototoxicity (may be severe) • Nephrotoxicity (may be severe), proteinuria • Electrolyte abnormalities • Diarrhea • Anorexia • Rash (may be severe)	• Hemolytic uremic syndrome, vasculitis • Hemolysis • Pneumonitis, ARDS • Capillary leak syndrome • Arrhythmia • Cardiotoxicity • Arterial thromboembolism • Venous thromboembolism • Secondary malignancy • Seizures • PRES • Hypersensitivity

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; baseline and regular
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Audiogram; baseline as clinically indicated
- Clinical toxicity assessment (infection, bleeding, flu-like symptoms, lethargy, dyspnea, rash, nausea/vomiting and other GI effects, neurotoxicity, ototoxicity); at each visit

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

Suggested Clinical Monitoring

INR for patient receiving warfarin; Baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	Day 1: 4 to 5 hours; Gemcitabine only day: 0.75 hour
Pharmacy Workload (average time per visit)	31.387 minutes
Nursing Workload (average time per visit)	40.000 minutes

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K - References

Cisplatin, gemcitabine drug monographs, Cancer Care Ontario.

Lippert CM, Koser M, Wechsel H, et. al. Preliminary results of a phase II study of gemcitabine (G) plus cisplatin (C) in advanced or metastatic transitional cell carcinoma of the urothelium in a 21-day regimen. European Society for Medical Oncology. Annals of Oncology 2000; 11(4):79.

Moore M, Winquist E, Murray N, et. al. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer. A phase II trial of the NCIC Clinical Trials Group. J Clin Oncol 1999;17:2876-2881.

Roberts JT, von der Maase H, Sengeløv L, et al. Long-term survival results of a randomized trial comparing gemcitabine/cisplatin and methotrexate/vinblastine/doxorubicin/cisplatin in patients with locally advanced and metastatic bladder cancer. Ann Oncol 2006;17 Suppl 5:v118-22.

Soto Parra H, Cavina R, Latteri F, et al. Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study. Ann Oncol 2002;13(7):1080-6.

von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23(21):4602-8.

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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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

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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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