Regimen Monograph

A - Regimen Name

GEMC Regimen

Gemcitabine (Adjuvant)

Disease Site	Gastrointestinal Pancreas (Resectable)
Intent	Adjuvant
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	Adjuvant chemotherapy in patients with resectable pancreatic adenocarcinoma

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B - Drug Regimen

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

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

For a Usual Total of 6 Cycles, unless disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Febrile Neutropenia Risk: Low

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.

Dosage with toxicity

Doses should not be re-escalated if they are reduced for non-hematological toxicities, febrile neutropenia or thrombocytopenic bleeding.

Table 1 - Day 1 of Cycle:

Worst Toxicity in Previous Cycle	% Full Dose
Non-hematologic Grade 3**	75%*
Non-hematologic Grade 4	Consider discontinuing, or 50-75%*

Febrile neutropenia, thrombocytopenic bleeding	75%*
> 1 Occurrence of Day 8/15 holds	75%*
• Pneumonitis • Hemolytic Uremic Syndrome (HUS) • Stevens-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • Capillary Leak Syndrome (CLS) • Posterior reversible encephalopathy syndrome (PRES)	Discontinue

* Do not start new cycle until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and non-hematologic toxicity ≤ grade 2. Discontinue if non-hematological toxicities require more than a 50% dose reduction from the starting dose.

** except nausea/vomiting or alopecia

Other treatment days within cycle:

Table 2 - Non-hematologic toxicities

Toxicity	**Action (% Full dose)**
Grade 3**	HOLD; restart at 50-75%*
Grade 4	Discontinue

* Treat only if non-hematologic toxicities recover to ≤ grade 2 and hematologic parameters are met on treatment day (Table 3). Discontinue if non-hematological toxicities require more than a 50% dose reduction from the starting dose.

**except nausea/vomiting, alopecia

Table 3 - Hematologic Toxicities:

Platelets on treatment day (x 10^9/L)		**ANC on treatment day (x 10^9/L)**	**Action (% Full Dose)**
>100	And	> 1	100% *
50 to 100	And/or	0.5 to 1	75% or consider omit*
<50	And/or	<0.5	Omit

* Treat only if above parameters are met on treatment day and non-hematologic toxicities ≤ grade 2.

Hepatic Impairment

Gemcitabine should be used with caution in patients with hepatic impairment (cirrhosis, hepatitis, alcoholism, metastases, etc.); initial dose reduction should be considered if the patient is treated, especially in hyperbilirubinemia.

Suggested:

Bilirubin (micromol/L)	Starting dose
> 1.2 x ULN	800 mg/m2; escalate if tolerated

Renal Impairment

Gemcitabine should be used with caution in patients with renal insufficiency. There is insufficient information from clinical studies to allow clear dose recommendations for this patient population. Clinical trials with cisplatin mandated CrCl ≥ 60mL/min. For patients with pre-existing renal insufficiency, the close monitoring for occurrence of hemolytic uremic syndrome is required.

Dosage in the Elderly

Decreased clearance and increased half-life occurs with increasing age, however no dose adjustment is necessary.

Dosage based on Gender

Decreased volume of distribution and clearance are seen in women, however no dose adjustment is necessary.

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F - Adverse Effects

Refer to gemcitabine 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) • ↑ LFTs • Nausea/ vomiting (generally mild)	• Flu-like symptoms • Proteinuria • Rash (rarely severe)	• Edema • Musculoskeletal pain • Alopecia (generally mild) • Diarrhea	• Arrhythmia • Arterial thromboembolism • Cardiotoxicity • Hepatotoxicity including liver failure • Hemolytic-uremic syndrome • Creatinine increased • Hypersensitivity • Injection site reaction • Gangrene • RPLS/PRES • ILD/ARDS • Capillary leak syndrome • Vasculitis • Radiosensitization • Toxic epidermal necrolysis (TEN) • Stevens Johnson syndrome (SJS))

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G - Interactions

Refer to gemcitabine drug monograph(s) for additional details

- No specific drug interaction studies have been conducted.
- Monitor INR closely with concurrent warfarin use and adjust warfarin dose as needed, as

gemcitabine may decrease metabolism and synthesis of clotting factors.

- Gemcitabine is a known radiosensitizer.

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H - Drug Administration and Special Precautions

Refer to gemcitabine drug monograph(s) for additional details

Administration

- May dilute reconstituted drug in normal saline for IV infusion, resulting in a minimum final concentration of at least 0.1 mg/mL.
- Gemcitabine is for IV administration only and should be infused over 30 minutes.
- To prevent increased toxicity, avoid an infusion time of > 60 minutes or dosing more frequently than once weekly

Contraindications

- Patients who have a hypersensitivity to this drug or any of its components.

Other Warnings/Precautions

- Use with extreme caution in patients with compromised bone marrow reserve.
- Use with caution in patients with hepatic impairment (including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis) and patients with renal impairment.
- Acute shortness of breath with a temporal relationship to gemcitabine injection administration may occur.
- Patients receiving concurrent radiation while receiving the full dose gemcitabine should be closely monitored for reactions. Exacerbation of radiation therapy toxicity including potentially life-threatening esophagitis and pneumonitis, particularly in patients receiving large volumes of radiotherapy have been observed.

Pregnancy/Lactation

- Gemcitabine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months (general recommendation) after the last dose.
- Breastfeeding is not recommended.
- Fertility: Observed in animal studies
    - Decreased spermatogenesis and fertility in male mice.

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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 dose
- Liver function tests; Baseline, before each cycle and as clinically indicated
- Renal function tests; Baseline, before each cycle and as clinically indicated
- Clinical assessment of bleeding, infection, rash, diarrhea, nausea/vomiting, edema, injection site reactions, flu-like symptoms, hemolysis, signs/symptoms of capillary leak syndrome, cardiovascular, CNS and respiratory effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Urinalysis; baseline and as clinically indicated
- INR for patient receiving warfarin; baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	0.75 hour
Pharmacy Workload (average time per visit)	22.855 minutes
Nursing Workload (average time per visit)	36.667 minutes

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K - References

Gemcitabine drug monograph, Cancer Care Ontario.

Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer. A randomized controlled trial. JAMA 2007; 297:267-77.

PEBC Advice Documents or Guidelines

- Role of Adjuvant Treatment in Resected Pancreatic Ductal Adenocarcinoma

November 2022 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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