Regimen Monograph

A - Regimen Name

CISPGEMC Regimen

Gemcitabine-CISplatin

Disease Site	Unknown Primary
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.

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B - Drug Regimen

CISplatin	75 mg /m²	IV	Day 1
gemcitabine	1000 mg /m²	IV	Days 1, 8 and 15

Alternative schedule:

CISplatin	75 mg /m²	IV	Day 1

gemcitabine	1000 mg /m²	IV	Days 1 and 8

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C - Cycle Frequency

Standard schedule: **REPEAT EVERY 28 DAYS**

Alternative schedule: **REPEAT EVERY 21 DAYS**

Until disease progression or unacceptable toxicity, usually up to 6 cycles due to cumulative cisplatin toxicity

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D - Premedication and Supportive Measures

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

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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

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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 (% previous dose)	Cisplatin (% previous dose)

Grade 4 febrile neutropenia or thrombocytopenia	75%	75%
Grade 2 neurotoxicity/ototoxicity/nephrotoxicity	No change	75%
Grade 3 or 4 neurotoxicity/ototoxicity/nephrotoxicity	No change	Hold for current cycle; consider discontinuing
Other grade 3 non-hematologic related organ toxicity	75%	75%
Day 8 or day 15 holds in > 1 cycle	75%	No change
Grade 4 non-hematologic related organ, pneumonitis, hemolytic uremic syndrome, SJS/TEN, CLS, PRES, severe hypersensitivity	Discontinue	Discontinue

* Do not restart until ANC ≥1.5x 10^9/L, platelets ≥100 x 10^9/L and non-hematologic toxicity ≤ grade 2.

Dose on Day 8 or 15 of Cycle:

Toxicity on Day 8 or Day 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 50-75%
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

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

Dosage in the Elderly

CISplatin: Geriatric patients may be at higher risk of developing nephrotoxicity, ototoxicity/neurotoxicity or hematologic adverse effects with cisplatin.

gemcitabine: Clearance is lower in the elderly but no dose adjustment necessary.

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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 and bleeding (may be severe) · Fatigue, flu-like symptoms · Musculoskeletal pain · Nausea, vomiting · ↑ LFTs (may be severe) · Neurotoxicity · Ototoxicity · Nephrotoxicity (may be severe) · Electrolyte abnormalities · Diarrhea · Rash · Edema	· Cardiotoxicity, arrhthymia · Arterial thromboembolism · Hemolysis · Hemolytic uremic syndrome · Vasculitis · Hemolysis · Pneumonitis · Capillary leak syndrome · Seizures · PRES · Hypersensitivity · Secondary malignancy

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G - Interactions

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

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H - Drug Administration and Special Precautions

Refer to CISplatin, gemcitabine 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

- 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
- Clinical toxicity assessment (infection, bleeding, nausea/vomiting, neurotoxicity, ototoxicity, GI and CNS effects); regular

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

Suggested Clinical Monitoring

- Audiogram; baseline and periodic
- INR for patient receiving warfarin; baseline and regular
- Urinalysis; baseline and regular

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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 and gemcitabine drug monographs, Cancer Care Ontario.

Culine S, Lortholary A, Voigt JJ, et al; Trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). Cisplatin in combination with either gemcitabine or irinotecan in carcinomas of unknown primary site: results of a randomized phase II study--trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). J Clin Oncol. 2003 Sep 15;21(18):3479-82.

Gross-Goupil M, Fourcade A, Blot E, et al. Cisplatin alone or combined with gemcitabine in carcinomas of unknown primary: results of the randomised GEFCAPI 02 trial. Eur J Cancer. 2012 Mar;48(5):721-7.

Isik M, Seker MM, Odabas H, et al. Gemcitabine and cisplatin in patients with carcinoma of unknown primary site. Med Oncol 2011;28(2):591-6.

May 2019 Updated emetic risk category

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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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