Regimen Monograph

A - Regimen Name

CISPGEMC(W) Regimen

CISplatin-Gemcitabine

Disease Site	Gastrointestinal - Hepatobiliary / Liver / Bile Duct
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	Treatment of non-resectable or recurrent/metastatic biliary tract cancer (including cholangiocarcinoma, gallbladder, ampullary). The clinical trial included chemotherapy-naive patients with good performance status (ECOG 0-2).

back to top

B - Drug Regimen

CISplatin	25 mg /m²	IV	Days 1 and 8
gemcitabine	1000 mg /m²	IV	Days 1 and 8

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

Up to 8 cycles unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

All patients should receive adequate hydration and premedication for emesis, according to local guidelines.

back to top

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 (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%
Grade 4			Consider discontinuing, or ↓ to 50-75%[3]	Consider discontinuing, or ↓ to 50-75%[3]
> 1 occurrence of Day 8 holds			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
Posterior reversible encephalopathy syndrome (PRES)			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] 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)**	**Cisplatin (% 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 HUS SJS TEN CLS		-		-	Discontinue	Consider Discontinue
PRES		-		-	Discontinue	

Cisplatin - Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

There is insufficient evidence that routine prophylaxis with extended cisplatin infusion reduces IR rates.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms.	• Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge.

	Restart: • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.

* Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist)

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.

Bilirubin	Gemcitabine (Suggested Starting Dose)	Cisplatin
> 1.2 x ULN	Consider dose reduction (800 mg/m^2)	No dosage adjustment required

Renal Impairment

In some clinical trials, patients were not treated with cisplatin unless CrCl ≥ 45mL/min. If the benefit of continued treatment is clinically warranted, the following dose modifications could be considered at the physician's discretion:

Creatinine Clearance (mL/min)	Cisplatin (% previous dose)	Gemcitabine
46-60	75%	Use with caution; insufficient information for recommendation. Close monitoring for occurrence of hemolytic uremic syndrome is required.
30-45	50% or consider discontinuing	
< 30	Discontinue	

Dosage in the Elderly

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.

back to top

F - Adverse Effects

Refer to gemcitabine, CISplatin 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 (may be severe) • Nausea or vomiting	• Fatigue, flu-like symptoms • Nephrotoxicity (may be severe) • Abnormal electrolytes • Proteinuria • Neurotoxicity, ototoxicity • Rash (may be severe)	• Edema • Musculoskeletal pain • Alopecia (generally mild) • Diarrhea	• Pneumonitis/ARDS • Capillary leak syndrome • Posterior reversible encephalopathy syndrome • Leucoencephalopathy • Seizures • Optic neuritis/other eye disorders • Hyperuricemia • Hemolytic-uremic syndrome • Thrombotic microangiopathy • SIADH • Arterial and venous thromboembolism • Arrhythmia • Cardiotoxicity • Hypersensitivity • Injection site reaction • Toxic epidermal necrolysis • Stevens-Johnson syndrome

			• Radiosensitization • Vasculitis • Raynaud's • Secondary malignancy

back to top

G - Interactions

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

- Ascertain renal function prior to giving renally excreted drugs; monitor for toxicity
- Avoid nephrotoxic drugs; use with extreme caution during or shortly after cisplatin treatment (1 to 2 weeks)
- Avoid concomitant use of ototoxic drugs and cisplatin; use with extreme caution if essential
- Monitor serum levels for anticonvulsant agents (valproic acid, carbamazepine, phenytoin) when used with cisplatin, and adjust dose if necessary
- 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.

back to top

H - Drug Administration and Special Precautions

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

Administration – Cisplatin:

- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Drug dilution and infusion durations vary according to the regimen. Some centres dilute cisplatin in 500 mL NS.
- All patients should receive adequate hydration and premedication for emesis, according to local guidelines.
- Additional hydration may be ordered for hypovolemic patients.
- Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at discretion of physician.
- Adequate hydration and urinary output must be maintained for 24 hours following cisplatin treatment.

- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Administration – gemcitabine:

- 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 with known hypersensitivity to gemcitabine or platinum containing compounds
- Patients who are myelosuppressed (cisplatin)
- Patients with pre-existing renal impairment and hearing impairment, unless the possible benefits of treatment outweigh the risks (cisplatin)

Other Warnings/Precautions:

- Use gemcitabine with extreme caution in patients with compromised bone marrow reserve.
- Use gemcitabine 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 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:

- Cisplatin and gemcitabine are not recommended for use in pregnancy. Appropriate contraception should be used by both sexes during treatment, and for at least **6 months** in females (general recommendation) and **2 years** in males after the last dose.
- Male patients should not donate semen while using cisplatin and up to 2 years after the last dose.

- Breastfeeding is not recommended (cisplatin is secreted into breast milk).
- Fertility effects: Yes

back to top

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; baseline and before each cycle
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; baseline and before each cycle
- Audiogram; baseline and as clinically indicated
- Clinical toxicity assessment (infection, bleeding, flu-like symptoms, injection site reactions, fatigue, edema, rash, nausea/vomiting and other GI effects, neurotoxicity, ototoxicity, thromboembolism, signs/symptoms of capillary leak syndrome, cardiovascular or 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

back to top

J - Administrative Information

Approximate Patient Visit	3 hours
Pharmacy Workload (average time per visit)	34.104 minutes
Nursing Workload (average time per visit)	46.667 minutes

back to top

K - References

Cisplatin and gemcitabine drug monographs, Cancer Care Ontario.

Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 2006;24(24):3946-52.

Okusaka, T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010;103(4):469-74.

Valle J, Wason H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362(14):1273-81.

June 2021 Updated Dose Modifications, Adverse effects, Interactions, Drug administration and precautions and Monitoring sections

back to top

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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back to top