Regimen Monograph

A - Regimen Name

GDP Regimen

Gemcitabine-Dexamethasone-PLATINOL® (CISplatin)

Disease Site

Hematologic - Lymphoma - Non-Hodgkin's High Grade
Hematologic - Lymphoma - Non-Hodgkin's Intermediate Grade

Intent

Curative
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 treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma.

The clinical trial by Crump *et al* included patients with ECOG status 0 to 3; patients with diffuse large B-cell lymphoma who had received one previous anthracycline-containing chemotherapy regimen; and patients with DLBCL transformed from follicular or other indolent-histology lymphoma had received ≤ 3 previous treatments, with at least one anthracycline-containing regimen. Patients were cisplatin and gemcitabine naïve prior to treatment.

Supplementary	**dexamethasone**
Public Funding	ODB - General Benefit (dexamethasone) (ODB Formulary)

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B - Drug Regimen

gemcitabine	1000 mg /m²	IV	Days 1 and 8
CISplatin	75 mg /m²	IV	Day 1
dexamethasone	40 mg	PO	Days 1 to 4

(Outpatient prescription in 4mg tablets)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

- If complete or partial response occurs after 2 cycles, may proceed to autologous stem cell transplant (ASCT). May receive a third cycle if patient has not achieved a complete or partial response after 2 cycles.
- Patients with stable disease who were not candidates for stem cell transplant or patients who had any response after 2-3 cycles of GDP may receive up to 6 cycles of treatment.

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (D1)
Low (D8)

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

- The day 1 dexamethasone dose can be given IV before chemotherapy to prevent emesis, with the oral treatment dose reduced accordingly.

- Consider use of filgrastim to maintain dose intensity for patients with febrile neutropenia or prolonged neutropenia.
- Standard regimens for Cisplatin premedication and hydration should be followed. Refer to local 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. The following recommendations have been adapted from the LY.12 study (Crump *et al*, 2014).

Dosage with toxicity

Dose adjustments are to be made based on the system showing the greatest degree of toxicity. Doses held during a cycle of therapy do not need to be made up. All doses should go back to 100% of the planned dose for the next cycle, unless otherwise indicated below.

Table 1: Dosage with Hematologic Toxicities

Day(s) of Cycle	Absolute Neutrophil Count (ANC) ($x10^9$/L)		Platelets ($x10^9$/L)	Action This Cycle
Day 1	≥ 1.0	AND	≥ 75	Give 100% dose of all drugs
	≥ 1.0	AND	< 75	Delay 1 week* If platelets then ≥ 75, give 100% dose of all drugs. If platelets still < 75 but ≥ 50, give 100% dose rather than delay further; support with platelet transfusions as necessary.
	< 1.0	AND	≥ 75	Delay 1 week* If ANC then ≥ 1.0, give 100% of all drugs. If ANC still < 1.0 but ≥ 0.5, give 100%

				dose rather than delay further; initiate GCSF. **
	< 1.0	AND	< 75	Delay 1 week* • If ANC at that point ≥ 0.5 and platelets ≥ 50: give 100% of all drugs; initiate GCSF; support with platelet transfusions. OR • If ANC at that point < 0.5 and/ or platelets < 50: defer and check counts every 3-4 days. When both ANC ≥ 0.5 and platelets ≥ 50, resume as described above.
Day 8	≥ 1.0	AND	≥ 75	Give 100% dose of gemcitabine
	≥ 0.5 and < 1.0	AND	≥ 75	Give 100% dose gemcitabine and initiate GCSF* OR 75% of day 1 dose
	----		< 75 and ≥ 50	75% of day 1 dose
	< 0.5	OR	< 50	Omit gemcitabine dose this cycle and initiate GCSF **
* If counts presumed to be low due to marrow involvement, treat after 1-week delay (i.e. at 4 weeks or Day 28) despite counts. ** GCSF should be given prophylactically for all future cycles				

Table 2: Dosage with Non-Hematologic Toxicities

Serum creatinine must be ≤ 1.5 X ULN and bilirubin ≤ 1.5 X ULN prior to treatment at full dose. Refer to table below for dosing with elevated creatinine or bilirubin

If the toxicity is believed to be due to dexamethasone, then discontinue dexamethasone for that cycle and re-assess for future cycles.

Day(s) of Cycle	Worst grade in previous period		Gemcitabine	Cisplatin
Day 1	Hypersensitivity/ acute reactions grade 1-2		Hold causal agent for 1 hour then resume at 50% rate; monitor carefully	
	Hypersensitivity/acute reactions grade 3		Hold causal agent for 1 hour then resume at 50% rate. Monitor carefully If recurs discontinue causal agent	
	Hypersensitivity/acute reactions grade 4		Discontinue causal agent	
	≥ Grade 2 pneumonitis		Hold, if confirmed, discontinue	100%
	Grade 3 other toxicity *		75%	75%
	Creatinine	1.5 – 3.0 x ULN	100%	75% (for this and all future cycles)
		> 3.0 x ULN	Hold for one week; if recovers to ≤ 3 x ULN modify dose as above. If not discontinue	
	Bilirubin >	1.5 – 3.0 x ULN	75% (for this and all future cycles)	100%
		> 3.0 x ULN	Hold for one week; if recovers to ≤ 3 x ULN modify dose as above. If not, discontinue	
	Grade 4		Hold one week. If toxicity does not resolve to level acceptable for dose reduction (see above), discontinue treatment.	
Day 8	≤ Grade 2		100%	n/a
	≥ Grade 2 pneumonitis		Hold, if confirmed, discontinue	n/a
	Grade 3 other toxicity **		75% of day 1 dose	n/a
	Grade 4		Hold	n/a

* Except nausea, vomiting, and alopecia; In the event of grade 3 tinnitus, reduce cisplatin dose only. ** Patient may receive a dose reduction or discontinue treatment. This decision will depend upon the type of non-hematologic toxicity seen and is at the discretion of the treating physician.

Hepatic Impairment

See Table 2 above.

Renal Impairment

See Table 2 above.

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.

Dosage based on gender:

Gemcitabine clearance is lower in women but no dose adjustment is necessary.

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F - Adverse Effects

Refer to gemcitabine, CISplatin, dexamethasone 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 or bleeding (may be severe) • Nausea and vomiting • Fatigue and flu-like symptoms • Edema • ↑ LFTs (may be severe) • Alopecia • Neurotoxicity (including ototoxicity,may be severe) • Nephrotoxicity (including electrolyte abnormalities, may be severe and include SIADH), proteinuria • Diarrhea, stomatitis • Steroid effect (e.g. weight gain, hyperglycemia, gastric irritation, insomnia, mood changes) • Anorexia • Rash (may be severe) • Musculoskeletal pain • Reproductive effects	• Pneumonitis/ARDS • Capillary leak syndrome • Hemolytic-uremic syndrome, hemolysis • Arterial thromboembolism • Venous thromboembolism • Arrhythmia • Cardiotoxicity • Syncope • Vasculitis • Secondary malignancies • Hypersensitivity • Seizures • Raynaud's • RPLS (PRES), PML • Thrombotic microangiopathy • SIADH • Optic neuritis • Hyperviscosity • Steroid effects (e.g. cataracts, osteoporosis)

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G - Interactions

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

- Avoid nephrotoxic and ototoxic drugs (i.e. aminoglycosides) due to additive effects.
- Concomitant use of renally excreted drugs (i.e. methotrexate) may decrease renal clearance and enhance toxicities of these drugs. Avoid use, if possible. If not possible, modify doses as necessary.
- Cisplatin may decrease phenytoin levels; monitor levels and patient.
- Gemcitabine may increase INR and bleeding risk in patients taking warfarin; monitor closely and adjust INR as needed

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H - Drug Administration and Special Precautions

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

Administration

Gemcitabine:

- Dilute reconstituted drug in normal saline for IV infusion; to a minimum final concentration of 0.1 mg/mL.
- Infuse over 30 minutes through free-flowing IV.

Cisplatin:

- Ensure good urinary output during chemotherapy visit. Patient should void at least once during chemotherapy visit. Use locally approved hydration regimens.
- Blood pressure should be taken before and after chemotherapy.
- 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.
- 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.
- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur

Contraindications

- Patients with known hypersensitivity to gemcitabine or platinum containing compounds

Other Warnings/Precautions

- All patients should receive appropriate hydration and antiemetic protocols according to local guidelines.
- Gemcitabine use in patients with impaired hepatic function, including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the hepatic insufficiency
- Cisplatin and gemcitabine are not recommended for use in pregnancy or breastfeeding. Appropriate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose

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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

- Audiogram; Baseline and as clinically indicated
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; Baseline and before each dose
- CBC; Baseline and before each dose
- LFTs; baseline and before each cycle
- Renal function tests; Baseline and before each dose
- Clinical assessment of hypersensitivity reactions, tumour lysis syndrome, flu-like symptoms, infection, bleeding, GI (including nausea/vomiting), neurotoxicity, ototoxicity, thromboembolism, pulmonary, skin, CNS, cardiovascular side effects; At each visit

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

Suggested Clinical Monitoring

Audiogram; Periodic
Liver function tests; Baseline and regular
INR for patient receiving warfarin; Baseline and regular
Urinalysis; Baseline and regular

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J - Administrative Information

Approximate Patient Visit	Day 1: 4-5 hours; Day 8: 0.75 hour
Pharmacy Workload (average time per visit)	35.648 minutes
Nursing Workload (average time per visit)	44.167 minutes

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K - References

Cisplatin and gemcitabine drug monographs, Cancer Care Ontario.

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology b-cell non-hodgkin lymphoma. Cancer 2004;101(8):1835-42.

Crump M, Sherpherd K, Lin B. A randomized phase III study of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin as salvage chemotherapy followed by posttransplantation rituximab maintenance therapy versus observation for treatment of aggressive B-Cell and T-Cell non-Hodgkin's lymphoma. Clin Lymphoma 2005; 6(1): 56-60.

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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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