Regimen Monograph

A - Regimen Name

DHAP Regimen

Dexamethasone-High dose ARA-C (Cytarabine)-PLATINOL® (CISplatin)

Disease Site	Hematologic Lymphoma - Hodgkin Lymphoma - Non-Hodgkin's High Grade Lymphoma - Non-Hodgkin's Intermediate Grade
Intent	Curative
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 / refractory aggressive non-Hodgkin's lymphoma or Hodgkin's lymphoma, prior to autologous stem cell transplant (ASCT).
Supplementary Public Funding	**dexamethasone** ODB - General Benefit (dexamethasone) (tablets)

back to top

B - Drug Regimen

Adapted for outpatient administration

CISplatin	100 mg /m²	IV	Day 1
cytarabine	2000 mg /m²	IV	Q12H on Day 2 (total 2 doses)
dexamethasone	40 mg	PO	Days 1 to 4

back to top

C - Cycle Frequency

REPEAT EVERY 21 TO 28 DAYS

After 2-3 cycles, responding patients may be considered for high-dose chemotherapy and autologous stem cell transplant.

Patients with stable disease who were not candidates for stem cell transplant or patients who had any response after 2-3 cycles of DHAP may receive up to 6 cycles of treatment.

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: High

Febrile Neutropenia Risk: High

Other Supportive Care:

Also refer to CCO Antiemetic Summary

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

Cytarabine: dexamethasone eye drops 0.1% - instill 2 drops in each eye q 6 hour x 4 doses beginning 1 hour before the first dose of cytarabine, for 2 days.

back to top

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 LY12 protocol (Crump 2014).

Dosage with toxicity

Since this regimen is used as salvage therapy for potentially curative intent, it is recommended that modification of this regimen be done only after discussion with a medical oncologist experienced in the treatment of lymphoma.

Dosage with Hematologic Toxicity:

Blood counts on day 1		Blood counts on day 1	Cytarabine and cisplatin dose for this cycle
ANC ≥ 1	and	Platelets < 75	Delay 1 week* Restart at same dose if platelets ≥ 75[1] If platelets 50 to <75 after 1 week, may restart at same dose with platelet support as necessary[1]
ANC < 1	and	Platelets ≥ 75	Delay 1 week* Restart at same dose if ANC ≥ 1[1] If ANC ≥0.5 to <1, restart at same dose with G-CSF** support[1]
ANC < 1	and	Platelets < 75	Delay 1 week* After 1 week, if ANC > 0.5 and platelets > 50, restart at same dose with GCSF** and platelet support[1] OR If ANC < 0.5 and/ or platelets < 50, check counts q 3-4 days. When both ANC ≥ 0.5 and platelets ≥ 50, restart at same dose and with GCSF** and platelet support[1]

*If counts presumed to be low due to marrow involvement, treat after 1-week delay (e.g. at 4 weeks or Day 28) despite counts.

** GCSF should be given prophylactically for all future cycles

[1] Crump et al 2014

Dosage with Non-Hematologic Toxicity:

Worst Toxicity in Previous Cycle†	Cisplatin (% previous dose)* for this cycle	Cytarabine (% previous dose) for this cycle*	Dexamethasone
Grade 3 related non-hematologic toxicity, except nausea, vomiting, alopecia	Hold*, then 75%[1]	Hold*, then 75%[1]	No change
Creatinine 1.5 to 3 x ULN	75%	No change	No change
Grade 3 or 4 neurotoxicity /ototoxicity (cerebellar/ gait dysfunction related to cytarabine; sensory/peripheral)	Discontinue	Discontinue[1]	Discontinue
Other grade 4 non-hematologic/organ toxicity or creatinine > 3 x ULN	Hold for one week, hydrate. Discontinue if it does not resolve to ≤ grade 2[1]		
Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity reactions	Discontinue	Discontinue	Discontinue

[1] Crump et al 2014

† If toxicity is related to dexamethasone, may consider holding this drug for this cycle then re-assess for future cycles.

Hepatic Impairment

No dosage adjustment required for cisplatin. Cytarabine dose should be reduced with impaired hepatic function; no details available.

Renal Impairment

For cisplatin, renal function should have normalized before patients are retreated. If continued treatment is considered to be mandatory, the following dose modifications could be considered at the physician's discretion (Kintzel 1995).

Creatinine clearance	Cisplatin (% previous dose)
46-60	75%
30-45	50%
<30	Discontinue

For cytarabine, no adjustment required for standard doses. For high-dose therapy, since renal impairment (< 60 mL/min) is a risk factor for neurotoxicity, consider:

- dose reduction (2 g/m^2→ 1 g/m^2→ 0.1 g/m^2/day CIV)
- schedule modification (i.e. from q12h to q24h)

Dosage in the elderly

Geriatric patients may be at higher risk of developing nephrotoxicity, ototoxicity, neurotoxicity or hematologic adverse effects.

back to top

F - Adverse Effects

Refer to CISplatin, cytarabine, 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 / bleeding (may be severe) • Nausea and vomiting • Rash (may be severe) • Mucositis • Diarrhea (may be severe colitis) • Flu-like symptoms • ↑ LFTs • Hand-foot syndrome (may be severe) • Nephrotoxicity (may be severe) • Electrolyte abnormalities • Neurotoxicity and ototoxicity (may be severe) • Reproductive risk • Steroid effects (weight gain, myopathy, cataracts, hyperglycemia, gastric irritation, insomnia, mood changes, osteoporosis) • Alopecia • Fatigue • Anorexia • Conjunctivitis	• Arterial thromboembolism • Venous thromboembolism • Arrhythmia • Hemolytic uremic syndrome • Secondary malignancies • Hypersensitivity • Hemolysis • Optic neuritis • Vasculitis • Pancreatitis • Leukoencephalopathy • ARDS, pneumonitis • Tumor lysis syndrome • GI perforation • Thrombotic angiopathy • Syncope • SIADH

back to top

G - Interactions

Refer to CISplatin, cytarabine, 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.
- Cytarabine can decrease the efficacy of digoxin; monitor levels
- Cytarabine can decrease the effect of flucytosine; the dose of flucytosine should be increased
- Methotrexate IT can cause an increased risk of severe neurological effects when given with cytarabine IV; avoid concomitant administration
- Cyclophosphamide can cause increased cardiomyopathy and sudden death with high dose cytarabine; avoid the combination

back to top

H - Drug Administration and Special Precautions

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

Administration

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.

Cytarabine:

- May be mixed in 250mL bag (Normal Saline – preferred, or 5% dextrose)
- DO NOT use benzyl alcohol diluent with high dose cytarabine
- Incompatible with heparin, insulin, 5-fluorouracil, penicillin G and methylprednisolone sodium succinate.

Contraindications

- patients with known hypersensitivity to cytarabine or platinum containing compounds
- patients who are severely myelosuppressed
- patients with pre-existing renal impairment and hearing impairment, unless the possible benefits of treatment outweigh the risks.

Other Warnings/Precautions

- All patients should receive appropriate hydration and antiemetic protocols according to local guidelines.
- Extreme caution should be used with high dose cytarabine therapy, especially in older patients, patients with hepatic or renal impairment, pre-existing CNS, cardiovascular or pulmonary disease.
- Avoid live vaccines

Pregnancy/Breastfeeding

- This regimen is **contraindicated** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

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.

Note: high dose cytarabine regimens require intensive monitoring

Recommended Clinical Monitoring

- CBC; Baseline, and before each cycle (weekly is suggested)
- 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 of infection, bleeding, nausea/vomiting, neurotoxicity, ototoxicity, thromboembolism, GI, CNS, pulmonary, skin and ocular toxicity; at each visit

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

back to top

J - Administrative Information

Approximate Patient Visit	Inpatient regimen; some centres have modified this regimen for outpatient treatment.
Pharmacy Workload (average time per visit)	28.583 minutes
Nursing Workload (average time per visit)	44.167 minutes

back to top

K - References

Cisplatin and cytarabine drug monographs, Cancer Care Ontario.

Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 2014 Nov 1;32(31):3490-6.

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large B-cell lymphoma: a matched-pair analysis. Leuk Lymphoma. 2006 Dec;47(12):2558-66.

Olivieri A, Brunori M, Capelli D, et al. Salvage therapy with an outpatient DHAP schedule followed by PBSC transplantation in 79 lymphoma
patients: an intention to mobilize and transplant analysis. Eur J Haematol. 2004 Jan;72(1):10-7.

Press OW, Livingston R, Mortimer J, et al. Treatment of relapsed non-Hodgkin's lymphomas with dexamethasone, high-dose cytarabine, and cisplatin before marrow transplantation. J Clin Oncol 1991 Mar;9(3):423-31.

Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood. 1988 Jan;71(1):117-22.

Witzig TE, Geyer SM, Kurtin PJ, et al. Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: a phase II trial in the North Central Cancer Treatment Group. Leuk Lymphoma 2008 Jun;49(6):1074-80.

August 2023 Updated Drug Regimen section to be consistent with other DHAP regimens; Modified Pregnancy/lactation section

back to top

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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back to top