Regimen Monograph

A - Regimen Name

INOT Regimen

Inotuzumab

Disease Site

Hematologic
Leukemia - Acute Lymphoblastic (ALL)

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 Philadelphia chromosome (Ph)-positive and Ph-negative patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) who have good performance status (ECOG 0 to 2).

(For patients with Ph-positive ALL, failure with at least one second-generation or third-generation tyrosine kinase inhibitor (TKI) and standard multi-drug induction chemotherapy is required before treatment with inotuzumab ozogamicin (refer to NDFP form)

Supplementary Public Funding

inotuzumab ozogamicin
New Drug Funding Program (Inotuzumab Ozogamicin (Outpatient) - Relapsed or Refractory Acute Lymphoblastic Leukemia) (NDFP Website)

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B - Drug Regimen

Cycle 1:

inotuzumab ozogamicin	0.8 mg /m²	IV	Day 1

Then,

inotuzumab ozogamicin	0.5 mg /m²	IV	Days 8* and 15*

* +/- 2 days (maintain at least 6 days between doses)

Cycle 2 and onwards (depending on response):

For patients who achieved CR** or CRi^:

inotuzumab ozogamicin	0.5 mg /m²	IV	Days 1, 8* and 15*

For patients who **did not** achieve CR** or CRi^:

inotuzumab ozogamicin	0.8 mg /m²	IV	Day 1

Then,

inotuzumab ozogamicin	0.5 mg /m²	IV	Days 8* and 15*

** CR defined as < 5% blasts in bone marrow and absence of peripheral blood leukemic blasts, platelets **≥** 100 and ANC **≥** 1, and resolution of any extramedullary disease
^ CRi defined as < 5% blasts in bone marrow and absence of peripheral blood leukemic blasts, platelets **<** 100 and ANC **<** 1, and resolution of any extramedullary disease

* +/- 2 days (maintain at least 6 days between doses)

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C - Cycle Frequency

Cycle 1: 21-day cycle
(Cycle length may be extended up to 28 days for patients who achieve CR (complete remission) or CRi (complete remission with incomplete hematologic recovery), and/or to allow for recovery from toxicity.)

Subsequent cycles: Repeat every 28 days

Two cycles of treatment in total are recommended. Consider a total of 3 cycles for patients who do not achieve a CR or CRi and MRD negativity after 2 cycles.
For patients with CR or CRi and MRD negativity who are not proceeding with HSCT, may give up to 6 cycles.
Discontinue treatment if CR or CRi is **not** achieved within 3 cycles.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Hypokalemia, hypomagnesemia and hypocalcemia should be corrected before inotuzumab ozogamicin administration.

Patients at risk for tumour lysis syndrome should receive adequate hydration, prophylaxis and be monitored closely.

For patients with circulating lymphoblasts, cytoreduction is recommended prior to the first dose (to a peripheral blast count ≤ 10,000/mm^3) with a combination of hydroxyurea, steroids and/or vincristine.

Consider prophylactic anti-infectives.

Pre-medications (prophylaxis for infusion reaction):

- Corticosteroid, antipyretic, and antihistamine are recommended prior to each dose.

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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

Hematologic toxicities:

Doses within a treatment cycle (e.g. days 8 and/or 15) do not need to be held due to neutropenia or thrombocytopenia.

If prior to inotuzumab ozogamicin treatment:	Blood counts during cycle	Action (for next cycle)
ANC ≥ 1 x 10^9/L	ANC decreases	Hold next cycle until ANC ≥ 1 x 10^9/L
Platelets ≥ 50 x 10^9/L*	Platelet count decreases	Hold next cycle until Platelets ≥ 50 x 10^9/L
ANC < 1 x 10^9/L and/or platelets* < 50 x 10^9/L	ANC or platelet count decreases	Hold next cycle until at least one of the following occurs: • ANC and platelet count recover to at least baseline for prior cycle • ANC ≥ 1 x 10^9/Land platelets ≥ 50 x 10^9/L • Stable or improved disease** and ANC and platelet decreases are due to underlying disease (not considered to be treatment-related)

*platelet count used for dosing should be independent of transfusion.
**based on most recent bone marrow assessment

Non-hematologic toxicities:

Dose interruptions within a cycle (e.g. days 8 and/or 15) are recommended for non-hematologic toxicities.

Non-Hematologic Toxicity	Action	Dosing at Restart (if applicable)			
		If dose held for ≤ 7 days (within a cycle)	**If dose held for ≥ 7 days**	**If dose held for ≥ 14 days**	**If dose held for > 28 days**
Bilirubin > 1.5 x ULN and AST/ALT > 2.5 x ULN	Hold until Bilirubin ≤ 1.5 x ULN and AST/ALT ≤ 2.5 x ULN (except in Gilbert's syndrome or hemolysis)	Hold next dose (maintain a minimum of 6 days between doses)	Omit next dose within the cycle	↓ total dose by 25% for the subsequent cycle. 2nd occurrence: Reduce the number of doses to 2 per cycle for subsequent cycles. 3rd occurrence: Discontinue	Discontinue
Other ≥ Grade 2 non-hematologic	Hold until ≤grade 1 or baseline before each dose				
VOD/SOS or other severe liver toxicity	Discontinue	Not applicable			

Management of Infusion-related reactions:

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

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:**	• Re-challenge with pre-medications and at a reduced infusion rate of 50% at which the IR occurred. • Consider adding montelukast

	• Once symptoms have resolved, the infusion may be restarted at a reduced infusion rate (ie. 50% at which IR occurred).	± acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Permanently discontinue (do not re-challenge).

Hepatic Impairment

Bilirubin		**AST/ALT**	**Starting Dose**
≤ 1.5 x ULN	and	≤ 2.5 x ULN	No adjustment required
> 1.5 x ULN	and	> 2.5 x ULN	Limited data; if not due to Gilbert's syndrome or hemolysis, do not treat.

Renal Impairment

Creatinine Clearance (mL/min)	**Starting Dose**
≥ 30 (mild to moderate)	No adjustment required
15 to 29 (severe)	Limited data; use with caution
ESRD	No data

Dosage in the Elderly

No adjustment in starting dose is needed. No overall safety and efficacy differences between patients who were < 65 or ≥ 65 years of age. Increased age was associated with an increased risk of VOD/SOS after hematopoietic stem cell transplant.

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F - Adverse Effects

Refer to inotuzumab ozogamicin 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)	• Fatigue • Fever, chills • Nausea, vomiting • Headache • ↑ LFTs (may be severe)	• VOD / SOS • Abdominal pain • Diarrhea • Constipation • Mucositis • Anorexia	• Infusion-related reaction • QT/PR prolongation • ↑ Amylase / lipase • Tumour lysis syndrome

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G - Interactions

Refer to inotuzumab ozogamicin drug monograph(s) for additional details

- If possible, discontinue other QT prolonging drugs and use alternatives that do not prolong QT. If unavoidable, monitor closely.
- Avoid drugs that decrease electrolyte levels, if possible.

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H - Drug Administration and Special Precautions

Refer to inotuzumab ozogamicin drug monograph(s) for additional details

Administration

- Inotuzumab ozogamicin is light sensitive; **protect from light** during reconstitution, dilution and administration.
- Reconstitute inotuzumab ozogamicin using sterile water for injection according to instructions in the product monograph.
- Further dilute the reconstituted drug in 0.9% sodium chloride solution, to a total volume of 50mL. Final concentration should be between 0.01 to 0.1 mg/mL.
- Do not shake the drug. Gently invert the drug container to mix.
- The diluted solution does not require filtration. If a filter is needed, polyethersulfone (PES), polyvinylidene fluoride (PVDF) or hydrophilic polysulfone (HPS)-based filters are recommended. Do not use filters made of nylon or mixed cellulose ester (MCE).
- Compatible with PVC, (DEHP or non-DEHP containing), polyolefin, or ethylene vinyl acetate (EVA) containers or infusion lines.
- The diluted solution may be refrigerated or stored at room temperature. (Refer to the product monograph for storage times.)
- If the diluted solution is refrigerated, it should remain at room temperature for about 1 hour before administration (protect from light).
- Infuse the diluted solution for 1 hour at a rate of 50 mL/hour.
- During administration, protect the infusion bag from light using an UV light-blocking cover (e.g. amber, dark brown or green bags or aluminum foil). The infusion line does not need to be protected from light.

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

Contraindications:

- Hypersensitivity to this drug or to any of its components

Other Warnings/Precautions:

- Not recommended for use in CD22-negative B-cell precursor ALL patients
- Use with caution in:
    - patients with a history of or risk factors for QTc prolongation or Torsade de pointes, who are taking medications known to prolong the QT interval, or

  - have electrolyte disturbances or pre-existing conduction system abnormalities, or
  - patients who have experienced prior VOD/SOS or patients with ongoing severe liver disease, or
  - patients who are older, have had a previous HSCT, in later lines of salvage and/or a previous history of liver disease and/or hepatitis

- Avoid using conditioning regimens containing 2 alkylating agents, to decrease risk of VOD/SOS after HSCT.
- Vaccination with live vaccines is not recommended for at least 2 weeks before starting inotuzumab ozogamicin treatment, during treatment and until B-lymphocyte recovery after the final cycle.
- Inotuzumab ozogamicin has moderate influence on the ability to drive and use machines. Caution is recommended when performing these activities as patients may experience fatigue during treatment.

Pregnancy/Lactation:

- Inotuzumab ozogamicin is not recommended for use in pregnancy. Female patients (and their male partners) should use adequate contraception during treatment, and for at least 8 months after the last dose. Male patients with partners of childbearing potential should use adequate contraception during treatment and for at least 5 months after the last dose.
- Breastfeeding is not recommended during treatment and for at least 2 months after the last dose.
- Fertility may be impaired.

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; Baseline and before each dose
- Liver function tests; Baseline, before and after each dose; more frequent if hepatotoxicity is suspected
- Renal function tests; Baseline and before each cycle
- Electrolytes; Baseline and as clinically indicated
- Amylase and lipase; Baseline and as clinically indicated
- ECGs; Baseline and as clinically indicated; more frequent in patients at risk of

prolonged QT/PR
- Infusion reactions; During and for at least 1 hour after the infusion
- Clinical toxicity assessment for tumour lysis syndrome, infection, bleeding, fatigue, GI effects, VOD/SOS; At each visit
- Post-HSCT patients; Monitor closely for hepatotoxicity and infection. Monitor liver function tests closely during the first month post-HSCT, then less frequently after

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

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J - Administrative Information

Approximate Patient Visit	2 hours
Pharmacy Workload (average time per visit)	26.35 minutes
Nursing Workload (average time per visit)	49.833 minutes

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K - References

Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016 Aug 25;375(8):740-53.

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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