Regimen Monograph

A - Regimen Name

AZCT Regimen

Azacitidine

Disease Site

Hematologic
- Leukemia - Acute Myeloid (AML)
- Myelodysplastic Syndrome (MDS)
- Myeloproliferative Neoplasms (MPNs)

(CMML)

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 adult patients with intermediate-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS), and who are not eligible for hematopoietic stem cell transplantation
- Adults with Acute Myeloid Leukemia (AML), with 20-30% blasts and multi-lineage dysplasia, according to the WHO classification who are not eligible for stem cell transplant
- Treatment of older patients with newly diagnosed AML with > 30% bone marrow blasts without immediate intent for hematopoietic stem cell transplant (HSCT) or who are unfit for induction chemotherapy

Supplementary Public Funding	**azaCITIDine** New Drug Funding Program (Azacitidine - Intermediate-2 and high-risk myelodysplastic syndrome (MDS)) **azaCITIDine** New Drug Funding Program (Azacitidine - Acute Myeloid Leukemia (AML)) **azaCITIDine** New Drug Funding Program (Azacitidine - Acute Myeloid Leukemia (AML) Greater Than 30% Blasts)
Additional Information	**The information provided in this document is intended for use only in the management of adults with leukemia/ MDS /MPN, and for cancer centres with expertise in treating acute leukemia/ MDS/ MPN.**

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B - Drug Regimen

Azacitidine for injection is **not interchangeable** with, and should not be substituted with or for, azacitidine tablets. Verify drug name, dose, and administration route. The different dosage forms are not bioequivalent.

azaCITIDine	75 mg /m²	Subcut	Daily; Days 1 to 7

Alternative Schedule:

azaCITIDine	75 mg /m²	Subcut	Daily on days 1-5 and 8-9 (5-2-2 regimen)

Alternative Schedule:

azaCITIDine	75 mg /m²	Subcut	Daily; Days 1 to 6

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C - Cycle Frequency

REPEAT EVERY 28 DAYS in the absence of disease progression or unacceptable toxicity, for a minimum of 6 cycles

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Other Supportive Care:

- Consider appropriate prophylaxis and close monitoring for patients at risk of tumour lysis syndrome (i.e. high tumour burden).
- Consider the use of supportive measures such as prophylactic antibiotics, transfusion and/or growth factors, according to local practice.

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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

Non-hematologic

Toxicity	Action
Differentiation syndrome	If suspected, initiate high-dose IV corticosteroids and hemodynamic monitoring. Consider temporary hold of azacitidine until symptoms resolve; resume with caution.
Necrotising fasciitis	Discontinue

Renal tubular acidosis (low serum bicarbonate, increasing creatinine)	Reduce or delay next dose
Other severe drug related toxicity	Consider dose reduction or discontinuation

Hematologic

Normal baseline counts (X 10^9/L; WBC ≥ 3 and ANC ≥ 1.5 and platelets ≥ 75):

Table 1:

Nadir Counts			% Dose in the next cycle
ANC (*X 10^9/L*)		Platelets (*X 10^9/L*)	
≤ 1	and/or	≤ 50	Delay until recovery* then 50% if recovery requires > 14 days
> 1	and/or	> 50	Delay until recovery* then 100%

* Recovery = Counts ≥ Nadir count + (0.5 x {Baseline count – Nadir count})

Low baseline counts (X 10^9/L; WBC < 3 or ANC < 1.5 or platelets < 75):

Table 2:

↓ ANC or WBC or platelets from baseline		Improvement in any cell line differentiation?	Action	Recovery* within 14 days?	Action
< 50%			Treat on time with no ↓ in dose	N/A	N/A
> 50%	And	Yes	Treat on time with no ↓ in dose	N/A	N/A
> 50%	And	No	Hold until recovery*	Yes	No ↓ in dose
> 50%	And	No	Hold until recovery*	No	Check marrow cellularity (Table 3)

* Recovery = Counts ≥ Nadir count + (0.5 x {Baseline count – Nadir count})

Table 3:

Bone marrow cellularity (Refer to Table 2)	Action and % Dose in next cycle if recovery* is not achieved within 14 days	
	Recovery ≤ 21 days	Recovery > 21 days
> 50%	No dose adjustment needed	
15 – 50%	Hold until recovery*; 100%	Hold until recovery*; 50%
< 15%	Hold until recovery*; 100%	Hold until recovery*; 33%

* Recovery = Counts ≥ Nadir count + (0.5 x {Baseline count – Nadir count })

Hepatic Impairment

Treat with caution. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours and has not been studied in patients with hepatic impairment.

Renal Impairment

Monitor patients with renal impairment closely as azacitidine and its metabolites are primarily excreted renally. Azacitidine can be administered to patients with renal impairment without initial dose adjustment. Subsequent dosage modifications should be made if reductions in serum bicarbonate levels and/or elevations in serum creatinine or BUN occur. The following are suggested modifications.

Creatinine / BUN		Serum bicarbonate (mmol/L)	Action and Dose (% previous dose)
≥ 2x ULN	and/or	< 20	There are no specific recommendations for dose reductions if present prior to starting azacitidine.
< 2 x ULN	and	< 20	50% on next cycle
≥ 2 X above baseline	and	any	Delay until normal or to baseline; 50% on next cycle

Dosage in the Elderly

No overall differences in safety or effectiveness were observed between younger patients and patients ≥ 65 years. Monitor closely as elderly patients are more likely to have deceased renal function or possibly greater sensitivity to the drug.

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F - Adverse Effects

Refer to azacitidine 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
• Nausea, vomiting • Myelosuppression ± infection, bleeding (May be severe) • Constipation	• Injection site reaction (may be severe) • Diarrhea • Dyspnea	• Fatigue • Headache • Musculoskeletal pain • Anorexia, weight loss • Dizziness • Rash (may be severe)	• Atrial fibrillation • Cardiotoxicity • Venous thromboembolism • Hypersensitivity • Hepatotoxicity • GI perforation • Pancreatitis • Pneumonitis • Nephrotoxicity • Renal tubular acidosis • Seizure • Tumor lysis syndrome • Leucocytoclastic vasculitis • Necrotizing fasciitis • Acute febrile neutrophilic dermatosis • Pyoderma gangrenosum • Differentiation syndrome

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G - Interactions

Refer to azacitidine drug monograph(s) for additional details.

- No formal clinical drug interactions have been studied with azacitidine.
- Azacitidine does not appear to induce or inhibit CYP 450.
- Use with caution in patients taking other medications known to prolong QTc.

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H - Drug Administration and Special Precautions

Refer to azaCITIDine drug monograph(s) for additional details.

Administration

Azacitidine for injection is **not interchangeable** with, and should not be substituted with or for, azacitidine tablets. Verify drug name, dose, and administration route. The different dosage forms are not bioequivalent.

- For subcutaneous use only. The manufacturer recommends using a fresh 25-gauge subcutaneous needle for injection.
- Follow local guidelines on maximum volumes for subcut injections. The manufacturer recommends that each syringe can contain up to 100 mg (4 mL) of azacitidine; doses greater than 4 mL should be injected into at least 2 separate sites.
- Discard if the drug contains large particles or agglomerates.
- Do not filter the suspension after reconstitution.
- Before injection, ensure contents of syringe are at room temperature. Contents of the syringe must be re-suspended immediately prior to administration, by vigorously rolling the syringe between the palms until a uniform cloudy suspension is achieved.
- Rotate injection sites; possible sites include the upper arm, thigh or abdomen.
- Do not inject into sites which are red, bruised, tender, or hardened.
- New injections should be given at least 2.5 cm from the previous site.
- If a dose is missed, it should not be given at the same time as the next dose, but should be added to the end of the current dosing cycle.
- Store unopened vials at room temperature (15 to 30°C).

Contraindications

- Patients who are hypersensitive to this drug or any of its components
- Patients with advanced, malignant hepatic tumours

Warnings/Precautions

- Use with caution in patients with poor performance status, extensive disease or significant cardiac or lung disease
- Safety and efficacy have not been established in patients with severe CHF, clinically unstable heart or lung disease.

Pregnancy/Lactation

- This regimen is not recommended 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).
- Fertility Effects: Probable

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; baseline, before each cycle and as clinically indicated (to monitor response and toxicity)
- Liver function tests; baseline and before each cycle
- Renal function tests; baseline and before each cycle
- Electrolytes and bicarbonate levels; baseline and before each cycle
- Clinical toxicity assessment for differentiation syndrome, bleeding, infection, cardiac, skin/local, neurological, venous thromboembolism, GI and tumour lysis effects; at each visit

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

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	11.879 minutes
Nursing Workload (average time per visit)	27.5 minutes

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K - References

Azacitidine drug monograph, Ontario Health (Cancer Care Ontario).

Fenaux P, Gattermann N, Seymour JF et al. Prolonged survival with improved tolerability in higher-risk myelodysplastic syndromes: azacitidine compared with low dose ara-C. Br J Haematol 2010; 149: 244–9.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. Lancet Oncol 2009; 10: 223-32.

Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. J Clin Oncol 2009;27(11):1850-6.

Sudan N, Rossetti JM, Shadduck RK, et al. Treatment of acute myelogenous leukemia with outpatient azacitidine. Cancer. 2006 Oct 15;107(8):1839-43.

PEBC Advice Documents or Guidelines

- Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

July 2023 Updated dose modifications, adverse effects, drug administration/special precautions, and monitoring sections

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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.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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