Regimen Monograph

A - Regimen Name

AZCT(MNT-PO) Regimen

Azacitidine maintenance

Disease Site

Hematologic
Leukemia - Acute Myeloid (AML)

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

For maintenance treatment in patients with newly diagnosed AML* who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation.

*de novo or secondary to prior myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), with intermediate- or poor-risk cytogenetics

Supplementary Public Funding	**azaCITIDine (tablets)** Exceptional Access Program (azaCITIDine (tablets) - For maintenance therapy in adult patients with AML who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation) (EAP Website)

back to top

B - Drug Regimen

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

Oral azacitidine should be started within 4 months of achieving CR or CRi.

azaCITIDine (tablets)	300 mg	PO	Daily on days 1 to 14

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen:	Moderate – Consider prophylaxis daily (Administer an antiemetic 30 minutes prior to each dose of azacitidine for the first 2 cycles. Administer antiemetic prophylaxis as needed after 2 cycles if there has been no nausea and vomiting.)

- 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 the use of granulocyte colony stimulating factor (GCSF) as clinically indicated.
- Consider the use of antidiarrheal medication for prophylaxis against diarrhea and for prompt treatment at the onset of symptoms.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

At the start of each cycle, initiate azacitidine only when ANC ≥ 0.5 x 10^9/L.

Dosage with toxicity

Dose Level	Azacitidine (tablets) Dose (mg/day)
0	300
-1	200

Toxicity	Criteria	Occurrence	Action
Neutropenia	ANC < 0.5 x 10^9/L OR ANC < 0.5-1 x 10^9/L with fever	First	Hold; consider use of GCSF as clinically indicated. Resume at same dose after recovery to ≤ grade 2.
		2 Consecutive Cycles	Hold; consider use of GCSF as clinically indicated. Resume at ↓ 1 dose level after recovery to ≤ grade 2.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days). Consider use of GCSF as clinically indicated.

		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.
Thrombocytopenia	Platelets < 25 x 10^9/L OR Platelets < 25-50 x 10^9/L with bleeding	First	Hold; resume at same dose after recovery to ≤ grade 2.
		2 Consecutive Cycles	Hold; resume at ↓ 1 dose level after recovery to ≤ grade 2.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days).
		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.
Nausea, Vomiting or Diarrhea	≥ Grade 3	First	Hold; resume at same dose after recovery to ≤ grade 1.
		Second	Hold; resume at ↓ 1 dose level after recovery to ≤ grade 1.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days).
		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.
All other nonhematologic toxicities	≥ Grade 3	First	Hold and provide medical support; resume at same dose after recovery to ≤ grade 1.
		Second	Hold; resume at ↓ 1 dose level after recovery to ≤ grade 1.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days).
		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.

Hepatic Impairment

Hepatic Impairment	Azacitidine (tablets) Dose (mg/day)
Mild impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 1.5 x ULN and any AST)	No dose adjustment is required
Moderate impairment (total bilirubin >1.5 to 3 x ULN)	Dose adjustment has not been established
Severe impairment (total bilirubin >3 x ULN)	Has not been studied

Renal Impairment

Creatinine Clearance (mL/min)	Azacitidine (tablets) Dose (mg/day)
≥30	No dose adjustment is required
<30	No initial dose adjustment required; monitor patients more frequently and modify dosage for adverse reactions.

Dosage in the Elderly

No dose adjustment is required. No overall differences in safety or effectiveness were observed between younger patients and patients ≥ 65 years.

back to top

F - Adverse Effects

Refer to azaCITIDine (tablets) 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 • Diarrhea	• Myelosuppression ± infection, bleeding (may be severe) • Constipation • Fatigue	• Musculoskeletal pain • Abdominal pain • Anorexia, weight loss • Dizziness	• Venous thromboembolism • Cardiotoxicity • Atrial fibrillation • Pneumonitis • GI perforation • Hepatotoxicity • Renal failure • Leukocytoclastic vasculitis • Pyoderma gangrenosum • Acute febrile neutrophilic dermatosis • Necrotizing fasciitis • Pancreatitis • Seizure • Tumor lysis syndrome • Differentiation syndrome

back to top

G - Interactions

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

- No clinically relevant drug-drug interactions is expected when azacitidine tablets are coadministered with CYP or transporter inhibitors, inducers or substrates.

back to top

H - Drug Administration and Special Precautions

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

Administration

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

- Take with or without food at approximately the same time each day.
- Swallow tablets whole with water. Do not split, crush or chew the tablets.
- If a dose of azacitidine is missed, administer the dose as soon as possible on the same day, and return to the normal time of dose administration the following day. Do not take 2 doses on the same day.
- If a dose is vomited, do not take another dose on the same day, return to the normal time of dose administration the following day.
- Store blisters at 15º to 30ºC. Store in the original aluminum blisters.

Contraindications

- Patients who are hypersensitive to the drug or to any component in the formulation.
- Patients with advanced malignant hepatic tumors.

Other Warning/Precautions

- **DO NOT** substitute azacitidine tablets for intravenous or subcutaneous azacitidine. There are substantial differences in the pharmacokinetic parameters. The recommended dose and schedule of azacitidine tablets are different from those of the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of azacitidine tablets may result in a fatal adverse reaction. Treatment of patients using azacitidine tablets at the doses recommended for intravenous or subcutaneous azacitidine may not be effective.
- The safety and effectiveness of azacitidine tablets for treatment of myelodysplastic syndromes have not been established. A higher incidence of early fatal and/or serious adverse reactions was observed in clinical trials. Treatment of patients with myelodysplastic syndromes is not recommended outside of controlled trials.
- The safety and efficacy of azacitidine tablets in patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease have not been established as they were excluded from the pivotal clinical study.
- No thorough clinical QT/QTc study or in vitro studies were performed to rule out the effect of azacitidine tablets on QT prolongation. An *in vivo* safety pharmacology animal study reported increased QTc interval, but interpretation of the study is limited by confounding effects associated with toxicity.
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- Patients should be advised that they may experience effects such as fatigue and asthenia and caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

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 treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility Effects: Observed in animal studies

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.

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

Recommended Clinical Monitoring

- CBC; Every other week for the first 2 cycles (56 days), every other week for the next 2 cycles after any dose adjustment, then monthly before each cycle and as clinically indicated
- Renal function tests; Baseline, before each cycle and as clinically indicated, more frequently in patients with severe renal impairment (ClCr <30 mL/min)
- Liver function tests; Baseline, before each cycle and as clinically indicated
- Clinical toxicity assessment for infection, bleeding, fatigue, hyperuricemia, falls, and cardiovascular and gastrointestinal effects; Baseline and as clinically indicated

back to top

K - References

Onureg (azacitidine tablets) Drug Monograph. Ontario Health (Cancer Care Ontario)

Wei AH, Dohner H, Pocock C, et al. Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med 2020;383:2526-37.
DOI: 10.1056/NEJMoa2004444

July 2023 Updated adverse effects section; Added link to hepatitis B virus screening and management guideline

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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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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back to top