Regimen Monograph

A - Regimen Name

CYTA(HD)+MIDO Regimen

Cytarabine (high-dose) and Midostaurin

Disease Site	Hematologic - Leukemia - Acute Myeloid (AML)
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	Consolidation treatment for adult patients with newly diagnosed FLT-3 mutated acute myeloid leukemia (AML) after induction with cytarabine and daunorubicin. Note: Only patients < 60 years of age were included in the clinical trial.
Supplementary Public Funding	**midostaurin** Exceptional Access Program (First-line treatment of adult patients diagnosed with FLT3-mutated acute myeloid leukemia, in combination with specific standard induction followed by consolidation chemotherapy, according to clinical criteria) (**EAP only considers funding of outpatient midostaurin usage**)

back to top

B - Drug Regimen

cytarabine	3000 mg /m²	IV	q 12 hours on days 1, 3, 5
midostaurin	50 mg	PO	BID on days 8 to 21

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

For a usual total of 4 cycles unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

- The use of corticosteroid ophthalmic drops is recommended. In the clinical trial, 0.1% dexamethasone 2 drops in each eye QID was used (starting 6-12 hours before initiation of cytarabine and continuing for at least 24 hours after completion)

back to top

E - Dose Modifications

Each cycle should be given within 2 weeks of hematologic recovery (ANC ≥ 1 x 10^9/L and platelets ≥ 100 x 10^9/L), but not sooner than 4 weeks from the beginning of the previous cycle.

Dosage with toxicity

Dosage in myelosuppression: Modify according to protocol by which patient is being treated; must be under the care of a specialized hemato-oncologist.

Toxicity	Action
Pulmonary infiltrates (≥ Grade 3)	Hold midostaurin for remainder of cycle. Resume midostaurin at same dose when resolves to ≤ Grade 1
Other non-hematological (≥ Grade 3)	Hold midostaurin until toxicities resolved to ≤ Grade 2*, then resume at same dose.

* toxicities considered at least possibly related to midostaurin

Hepatic Impairment

Hepatic Impairment	Midostaurin Dose	Cytarabine Dose
Mild or Moderate (Child-Pugh A or B)	No dose adjustment needed	Reduce dose. Use with extreme caution (No details found).
Severe (Child-Pugh C and/or total bilirubin > 2.5 X ULN)	Caution (no data available)	Reduce dose. Use with extreme caution (No details found).

Renal Impairment

For high-dose cytarabine therapy, renal impairment (< 60 mL/min) is a risk factor for neurotoxicity.

Renal Impairmemt	Midostaurin Dose	Cytarabine Dose
Mild or Moderate (CrCl 30-59 mL/min)	No dose adjustment needed	Caution; consider dose reduction (to 2000 mg/m^2) or schedule modification (from q12h to q24h) to reduce risk of neurotoxicity
Severe (CrCl 15-29 mL/min or end-stage renal disease)	Caution; data is limited	Caution; consider dose reduction (to 1000 mg/m^2) or schedule modification (from q12h to q24h) to reduce risk of neurotoxicity

Dosage in the Elderly

- Based on population PK analysis from AML patients aged 20 to 94, age did not have a clinically meaningful effect on the clearance of midostaurin and its active metabolites. No dose adjustment is required.
- There is limited experience in patients aged 60-70 years, and no experience in patients > 70 years. In patients ≥ 60 years old, only use in patients eligible for intensive induction chemotherapy with adequate performance status and no significant comorbidities.

Dosage based on gender:

- In population PK analysis, gender did not have clinically meaningful effects on midostaurin clearance. No dose adjustment required.

Dosage based on ethnicity:

- No dose adjustment based on ethnicity required with midostaurin. No differences in PK profile was shown between Caucasian and Black patients. In healthy Japanese volunteers, PK profiles of midostaurin and metabolites are similar compared to PK studies in Caucasians and Blacks.

Children:

- There are limited data in pediatric patients and the safety and efficacy of midostaurin has not been established.
- The safety of cytarabine in infants (< 1 year) has not been established.

back to top

F - Adverse Effects

Refer to cytarabine, midostaurin 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
• ↑ LFTs (may be severe) • Nausea, vomiting	• Headache	• Mucositis • Musculoskeletal pain	• Neurotoxicity • Cardiomyopathy • Typhitis

• Myelosuppression ± infection, bleeding (may be severe)		• ↑ Na • Hyperglycemia • Abdominal pain • Hemorrhoids • Hyperhidrosis • INR / prothrombin time increased • Insomnia • Cytarabine syndrome (flu like symptoms, rash) • Pharyngolaryngeal pain • Adult respiratory distress syndrome (ARDS) • Alopecia • Diarrhea • QT interval prolonged • Tachycardia • Rash (may be severe) • Hand-foot syndrome (may be severe) • Anorexia • Eye problems (conjunctivitis, corneal toxicity) • Colitis (may be severe)	• Pleural/pericardial effusion • Thromboembolism • Interstitial lung disease, pneumonitis • Leukoencephalopathy • Hypertension • Pancreatitis • Anaphylactoid drug reaction

back to top

G - Interactions

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

- Avoid strong CYP3A4 inhibitors. If strong inhibitors must be used concomitantly, closely monitor for midostaurin toxicity, especially during the 1st week of each cycle.
- Avoid strong CYP3A4 inducers as they may decrease midostaurin exposure.
- Caution with drugs that may prolong QT due to additive effects and risk of torsade de pointes.
- Caution with CYP 3A4/5 drugs with narrow therapeutic index.

- Caution with drugs that disrupt electrolyte levels due to possible additive effects.
- Cytarabine may cause decreased absorption/efficacy of digoxin due to intestinal mucosa damage; monitor levels.

back to top

H - Drug Administration and Special Precautions

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

Administration

Cytarabine:

- DO NOT use benzyl alcohol diluent with high dose cytarabine.
- Doses may be mixed in 250mL bag (Normal Saline – preferred, or 5% dextrose); Infuse IV over 3 hours.
- Incompatible with heparin, insulin, 5-fluorouracil, penicillin G and methylprednisolone sodium succinate.
- Diluted, unpreserved cytarabine solutions should be used within 24 hours at room temperature. Refer to the cytarabine product monograph for longer-term stability information.

Midostaurin:

- Midostaurin should be taken orally, twice daily, approximately 12 hours apart.
- Take with food to help prevent nausea. Prophylactic antiemetics may be necessary.
- Swallow capsules whole with a glass of water. Do not open, crush, or chew capsules.
- If a dose is missed, it should be skipped and the next scheduled dose taken at the scheduled time.
- If vomiting occurs, no additional dose should be taken and the next scheduled dose should be taken at the scheduled time.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- Store in the original package at room temperature (not above 30ºC).
- Keep out of reach and sight of children and pets.

Contraindications/Precautions

- patients who have a hypersensitivity to cytarabine, midostaurin, or any of its components
- cytarabine formulation/diluent containing benzyl alcohol should not be used for intrathecal use, high dose regimens or in neonates
- 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
- caution in patients with increased risk for torsade de pointes and with concomitant QTc interval-prolonging drugs
- caution in patients at risk for heart failure
- Cytarabine and midostaurin are contraindicated in pregnancy and may be present in semen. If pregnancy is possible, adequate contraception should be used by both sexes during treatment and for at least 6 months after the last dose. It is unknown if midostaurin reduces the effectiveness of hormonal contraceptives; a barrier method should also be used.
- Breastfeeding is not recommended during treatment and for at least 4 months after stopping treatment.
- No formal fertility studies have been conducted in humans (cytarabine). Midostaurin was associated with reproductive toxicity in both males and females 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.

Recommended Clinical Monitoring

- Blood glucose; Baseline and at each visit
- CBC; Baseline and before each cycle; more frequently at treatment initiation
- Liver function tests; Baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- LVEF; Baseline and as clinically indicated, especially in patients with risk factors
- Clinical toxicity assessment for signs and symptoms of CNS, GI, pulmonary, skin, and ocular toxicity, infection and bleeding, and heart failure; Baseline and at each visit

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

Suggested Clinical Monitoring

INR, aPTT; Baseline and at each visit

back to top

J - Administrative Information

Midostaurin: outpatient prescription for home administration

Pharmacy Workload (average time per visit) 21.079 minutes
Nursing Workload (average time per visit) 86.667 minutes

back to top

K - References

Cancer Care Ontario: midostaurin and cytarabine drug monographs

Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017; 377:454-464.

October 2018 Added EAP funding info to midostaurin

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.

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.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top