

BC Cancer Protocol Summary for Therapy of FLT3+ Acute Myeloid Leukemia Using Midostaurin in Combination with Induction and Consolidation Chemotherapy

Protocol Code

[LKAMLMIDO](#)

Tumour Group

Leukemia/BMT

Contact Physician

Dr. David Sanford

ELIGIBILITY:

- Newly diagnosed acute myeloid leukemia (AML) with FLT3 mutation.
- Use in combination with cytarabine and daunorubicin (7 + 3) induction chemotherapy and high or intermediate dose cytarabine (HIDAC or INDAC) consolidation chemotherapy.

EXCLUSIONS:

- Symptomatic congestive heart failure
- Pregnancy

TESTS:

- ECG at baseline and on days 8, 10 and 21 of each cycle for QTc monitoring.
- Refer to induction and consolidation chemotherapy orders for general laboratory monitoring related to induction and consolidation chemotherapy.

PREMEDICATIONS:

- Consider antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA).
- Refer to current Leukemia/BMT program recommendations for antiviral, antifungal and antibiotic prophylaxis related to induction and consolidation chemotherapy.

TREATMENT:

| Drug | Dose | BC Cancer Administration Guideline |
|-------------|---|------------------------------------|
| midostaurin | 50 mg BID on days 8 to 21 of each cycle of induction and consolidation chemotherapy | PO |

- If bone marrow on day 14 of induction shows significant residual disease, may give second induction; hold midostaurin and restart on day 8 of second induction.
- Patients who have residual AML after a second cycle of induction chemotherapy should be discontinued from midostaurin therapy.
- If remission achieved after induction, start consolidation following count recovery (e.g. platelet count above $100 \times 10^9/L$ and ANC above $1.0 \times 10^9/L$), at least 28 days after the start of induction.
- Repeat consolidation for up to 3 cycles. Consolidation cycles should be a minimum of 28 days in duration.

DOSE MODIFICATIONS:

1. Pulmonary:

| Pulmonary infiltrates | Management |
|-----------------------|--|
| Grade 3/4 | <ul style="list-style-type: none">▪ Interrupt midostaurin for remainder of cycle.▪ Resume midostaurin at same dose when infiltrate resolves to Grade ≤ 1. |

2. Cardiac – QTc Prolongation:

| QTc interval* | Suggested Management |
|---------------|--|
| above 500 ms | <ul style="list-style-type: none"> ▪ Interrupt midostaurin for remainder of cycle. ▪ Discontinue other QTc-prolonging medications where possible. ▪ Check potassium and magnesium levels and correct any abnormalities. ▪ Resume midostaurin at full dose next cycle provided QTc below or equal to 470 ms. |
| 470 to 500 ms | <ul style="list-style-type: none"> ▪ Reduce midostaurin dose to 50 mg PO once daily for remainder of cycle. ▪ Discontinue other QTc-prolonging medications where possible. ▪ Check potassium and magnesium levels and correct any abnormalities. ▪ Resume midostaurin at full dose for the next cycle provided QTc below or equal to 470 ms. |
| 450 to 470 ms | <ul style="list-style-type: none"> ▪ Continue midostaurin at same dose. ▪ Discontinue other QTc-prolonging medications where possible. ▪ Check potassium and magnesium levels and correct any abnormalities. |

* calculated using the Bazett or Fridericia formula.

3. Other Adverse Reactions:

| Non-hematological toxicity | Management |
|----------------------------|---|
| Other Grade 3/4 | Interrupt midostaurin until toxicities considered at least possibly related to midostaurin have resolved to Grade \leq 2, then resume at same dose. |

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
 2. **QTc interval prolongation:** Increased frequency of QTc prolongation has been observed. ECG monitoring of QTc interval should be undertaken at baseline and periodically during midostaurin therapy as described above. Use caution in combination with other medications known to prolong the QTc interval. Keep electrolytes within normal limits.
 3. **Cardiac dysfunction:** Patients with symptomatic congestive heart failure were excluded from clinical trials. Cases of cardiac failure, some fatal, and decreases in left ventricular ejection fraction were observed in studies using a higher midostaurin dose of 100 mg PO BID. Patients should be assessed for signs and symptoms of heart failure at baseline and periodically during midostaurin treatment.
 4. **Pulmonary toxicity:** Cases of interstitial lung disease and pneumonitis, some fatal, have been observed. Patients should be monitored for pulmonary symptoms.
5. **Drug Interactions:**
- Strong CYP3A4 inducers (e.g., rifampin) can decrease midostaurin exposure and concomitant use should be avoided.
 - Strong CYP3A4 inhibitors (e.g. voriconazole, posaconazole) can increase midostaurin exposure and alternatives should be considered where possible. If concomitant use is required, patients should be closely monitored for midostaurin toxicity, especially during the first week of midostaurin treatment in each cycle of chemotherapy.
 - Grapefruit, grapefruit juice and products containing grapefruit extract may increase midostaurin exposure and should be avoided.

Call Dr. David Sanford or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Stone RM, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med* 2017;377(5):454-64.
2. Novartis Pharmaceuticals Canada Inc. RYDAPT® product monograph. Dorval, Quebec. 21 July 2017.
3. Supplement to: Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation. *N Engl J Med* 2017;377:454-64. Available from: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1614359/suppl_file/nejmoa1614359_appendix.pdf