

# BC Cancer Protocol Summary for Therapy of Myelodysplastic Syndrome and Acute Myeloid Leukemia using azaCITIDine

**Protocol Code**

LKMDSA

**Tumour Group**

Leukemia/BMT

**Contact Physician**

Dr. Tom Nevill

## ELIGIBILITY:

1. **Myelodysplastic syndrome (MDS)** and ineligible for ASCT or as a bridge to ASCT, with intermediate risk or higher.
2. **Newly diagnosed acute myeloid leukemia (AML)**, regardless of blast percentage:
  - 70 years or older, **or**
  - Unfit or refuse intensive chemotherapy, regardless of age
3. **Relapsed AML or MDS:**
  - After ASCT and with bone marrow blasts < 20%, **or**
  - More than 6 months after ASCT, and ineligible for intensive chemotherapy or clinical trial.
4. **Chronic myelomonocytic (CMML):**
  - CPSS score  $\geq 1$ , **or**
  - CPSS risk groups of Intermediate-1, Intermediate-2, or High

## Note:

Patients with MDS are eligible to receive decitabine/cedazuridine (ULKMDSDC) OR azaCITIDine (LKMDSA) but not sequential use of these agents except for intolerance or contraindications

## EXCLUSIONS:

- MDS with:
  - IPSS risk: Low, or Intermediate-1 without high risk mutation, or
  - IPSS-R risk: Low, or Intermediate with score < 3.5
- CMML with CPSS score 0 (i.e., low risk)
- Advanced hepatic tumours
- Patients who experienced progression during treatment with decitabine/cedazuridine (ULKMDSDC)

**TESTS:**

- Baseline: CBC and differential, platelets, serum creatinine, GGT, alkaline phosphatase, ALT, Bilirubin, LDH, Albumin, sodium, potassium, chloride, serum bicarbonate, urea, INR, PTT
- On day 1 of each cycle and then weekly: CBC and differential, serum creatinine, sodium, potassium, chloride, serum bicarbonate, GGT, alkaline phosphatase, ALT, LDH, Bilirubin, INR, PTT
- If clinically indicated on Day 3, 5 of treatment: CBC and differential, platelets (physician responsible to monitor results and advise on supportive treatment)

<b>WEEK 1</b>						
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
<b>CBC &amp; diff, other tests**</b>	–	<b>CBC &amp; diff</b>	–	<b>CBC &amp; diff</b>	–	–
<b>azaCITIDine</b>	<b>azaCITIDine</b>	<b>azaCITIDine</b>	<b>azaCITIDine</b>	<b>azaCITIDine</b>	<b>azaCITIDine *</b>	<b>azaCITIDine *</b>
<b>WEEK 2</b>						
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
<b>CBC &amp; diff*, other tests**</b>	–	–	–	–	–	–
<b>WEEK 3</b>						
Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
<b>CBC &amp; diff, other tests**</b>	–	–	–	–	–	–
<b>WEEK 4</b>						
Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
<b>CBC &amp; diff, other tests**</b>	–	–	–	–	–	–

\*For weekend interruptions (ie. azaCITIDine 5 on, 2 off, 2 on) these doses will be administered on Days 8 and 9 - (for this regimen proceed with doses 6 and 7 despite day 8 labs – physician responsible to monitor results and advise on supportive care)

\*\*serum creatinine, sodium, potassium, chloride, serum bicarbonate, GGT, alkaline phosphatase, ALT, LDH, Bilirubin (total and direct), INR, PTT

**PREMEDICATIONS:**

- ondansetron 8 mg PO 30 minutes prior to azaCITIDine
- If persistent nausea/vomiting, may repeat ondansetron 8 mg PO q8h prn
- May add prochlorperazine 10 mg PO q6h prn
- sennosides (e.g. SENOKOT) one tablet PO daily strongly recommended with each dose of azaCITIDine

**TREATMENT:**

Drug	Dose	BC Cancer Administration Guideline
<b><u>Standard regimen (preferred)</u></b>		
<b>azaCITIDine</b>	75 mg/m <sup>2</sup> /d x 7 days	subcutaneous*
	Or	
	50 mg/m <sup>2</sup> /d x 7 days	subcutaneous*
	Or	
	37.5 mg/m <sup>2</sup> /d x 7 days	subcutaneous*
<b><u>Alternative regimen</u></b> If treatment must be interrupted by weekends:		
<b>azaCITIDine</b>	75 mg/m <sup>2</sup> /d x 5 days, no treatment for 2 days†, then 75 mg/m <sup>2</sup> /d x 2 days	subcutaneous*
	Or	
	50 mg/m <sup>2</sup> /d x 5 days, no treatment for 2 days†, then 50 mg/m <sup>2</sup> /d x 2 days	subcutaneous*
	Or	
	37.5 mg/m <sup>2</sup> /d x 5 days, no treatment for 2 days†, then 37.5 mg/m <sup>2</sup> /d x 2 days	subcutaneous*

\* Administer doses greater than 4 mL as two syringes at two separate sites

† may interrupt for more than 2 days but every effort should be made to avoid scheduling over long weekends (e.g., over 3-4 days) or statutory holidays during the week. If unavoidable, it should aim to deliver a total of 7 days of treatment out of about 10 consecutive days; having breaks in therapy over these circumstances do not require CAP approval.

- Repeat every 28 days until disease progression
- A bone marrow exam with cytogenetic analysis is recommended after 4-6 cycles to fully evaluate response

## DOSE MODIFICATIONS:

### 1. Hematological

**Nadir count:** (nadir: days 10-17; recovery: days 28-31)

ANC (x10 <sup>9</sup> /L)	Dose
greater than 0.5	100%
<b>Duration of ANC Nadir below 0.5</b>	
4 weeks or less	100%
More than 4 weeks but less than 6 weeks	Extend dosing interval to 5 weeks
<ul style="list-style-type: none"><li>6 weeks or more</li><li>After interval extension and duration of nadir is still greater than 4 weeks.</li></ul>	Dose Reduction to next dosing option per treatment guidelines
8 weeks or greater	Bone marrow biopsy

### 2. Non-Hematological

Toxicity	Grade	Dose
Gastrointestinal	0-2	100%
Gastrointestinal – Abdominal pain, constipation, diarrhea	3 or greater	Dose Reduction to next dosing option per treatment guidelines

- Renal dysfunction:** If increases in BUN or serum creatinine (unexplained) occur, delay next cycle until values reach baseline or normal, then reduce dose by 50% for next treatment course.
- Hepatic dysfunction:** Not studied in patients with hepatic impairment; use caution. Contraindicated in patients with advanced malignant hepatic tumors.
- Dosage adjustment based on serum bicarbonate:** if serum bicarbonate falls to less than 20 mmol/L (unexplained decrease), reduce dose by 50% for the next treatment course.

## PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Hepatotoxic:** May be hepatotoxic, progressive hepatic coma leading to death has been reported (rare) in patients with extensive tumor burden, especially those with a baseline albumin less than 30 g/L.
3. **Renal Toxicity:** Serum creatinine elevations, renal tubular acidosis, and renal failure have been reported with combination chemotherapy; decrease or withhold dose for unexplained elevations in BUN or serum creatinine, or reductions in serum bicarbonate to less than 20 mmol/L.

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

## References:

1. Fenaux P, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009;10:223-332.
2. Lyons RM, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Onc* 2009;27(11):1850-6.
3. Dombret H, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* 2015;126(3):291-9.
4. Greenberg PL, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. *Blood* 2012;120(12): 2454-65.
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7. Craddock C, et al. Clinical activity of azacitidine in patients who relapse after allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica* 2016;101(7):879-83.
8. Schroeder T, et al. Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions--a retrospective multicenter analysis from the German Cooperative Transplant Study Group. *Biol Blood Marrow Transplant* 2015;21(4):653-60.
9. Ades L, et al., Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine. *Leuk Res* 2013;37(6):609-13.
10. Drummond, M.W., et al., A multi-centre phase 2 study of azacitidine in chronic myelomonocytic leukaemia. *Leukemia* 2014;28(7):1570-2.
11. Pleyer L, et al. Outcomes of patients with chronic myelomonocytic leukaemia treated with non-curative therapies: a retrospective cohort study. *Lancet Haematol* 2021;8(2):e135-e148.
12. Such E, et al., Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. *Blood*, 2013;121(15):3005-15.

## Appendix. Myelodysplastic syndrome risk groups for azaCITIDine therapy

IPSS	IPSS-R
Intermediate-2 Intermediate-1 plus one high risk mutation* High	Intermediate with score $\geq 3.5$ High Very high

\* E.g., *EZH2*, *ETV6*, *p53*, *RUNX1*, *CBL*, *IDH2*, *U2AF1*, *FLT3-ITD*, *PRPF8* or *ASXL1*