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
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBsAb, HBcoreAb
- 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)
- If clinically indicated: HBV viral load (see protocol SCHBV)

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

*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 7despite 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
Standard regimen (preferred)		
azaCITIDine	75 mg/m^2/d x 7 days	subcutaneous*
	Or	
	50 mg/m^2/d x 7 days	subcutaneous*
	Or	
	37.5 mg/m^2/d x 7 days	subcutaneous*
Alternative regimen If treatment must be interrupted by weekends:		
azaCITIDine	75 mg/m^2/d x 5 days, no treatment for 2 days†, then 75 mg/m^2/d x 2 days	subcutaneous*
	Or	
	50 mg/m^2/d x 5 days, no treatment for 2 days†, then 50 mg/m^2/d x 2 days	subcutaneous*
	Or	
	37.5 mg/m^2/d x 5 days, no treatment for 2 days†, then 37.5 mg/m^2/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 (x10^9/L)	Dose
greater than 0.5	100%
Duration of ANC Nadir below 0.5	
4 weeks or less	100%
More than 4 weeks but less than 6 weeks	Extend dosing interval to 5 weeks
• 6 weeks or more • After interval extension and duration of nadir is still greater than 4 weeks.	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

3. **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.

4. **Hepatic dysfunction**: Not studied in patients with hepatic impairment; use caution. Contraindicated in patients with advanced malignant hepatic tumors.

5. **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.
4. **Hepatitis B Reactivation:** Low risk of Hepatitis B reactivation. See SCHBV for monitoring requirements.

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:

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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.
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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 with score ≥ 3.5
Intermediate-1 plus one high risk mutation*	High
High	Very high

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