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

Protocol Code	*ULKMDSA*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Tom Nevill*

ELIGIBILITY:

- Patients ineligible for ASCT or as a bridge to ASCT with:
  - Myelodysplastic syndrome (MDS) according to WHO classification with:
    - IPSS intermediate-2 (including intermediate-1 plus one high risk-mutation involving EZH2, ETV6, p53, RUNX1, CBL, IDH2, U2AF1, FLT3-ITD, PRPF8 or ASXL1) and high risk, or
    - IPSS-Revised intermediate ≥ 3.5, high or very high risk
  - Newly diagnosed Acute Myeloid Leukemia (AML) according to WHO classification with ELN intermediate or high risk cytogenetics who are 65 years or older OR are, regardless of age, unfit for or refuse intensive chemotherapy
- Patients with AML or MDS relapsed after ASCT with:
  - Bone marrow blasts < 20% OR
  - Relapse > 6 months following ASCT, and ineligible for intensive chemotherapy or clinical trial.
- Patients with chronic myelomonocytic (CMML) with CPSS category of Int-1/Int-2/High risk (e.g. CPPS score ≥1)
- A BC Cancer "Compassionate Access Program" request with appropriate clinical information for each patient must be approved prior to treatment.

EXCLUSIONS:

- Hypersensitivity to azaCITIDine, mannitol, or any component of the formulation
- Advanced hepatic tumors

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)

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*

*** round dose to the nearest 0.1 mg*

† 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.

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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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.
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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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