

BCCA Protocol Summary for Therapy of Myelodysplastic Syndrome using Azacitidine

Protocol Code	<i>ULKMDSA</i>
Tumour Group	<i>Leukemia/BMT</i>
Contact Physician	<i>Dr. Tom Nevill</i>
Contact Pharmacist	<i>Judith Nyrose</i>

ELIGIBILITY:

For the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with:

- International Prognostic Scoring System (IPSS) intermediate-2 and high-risk Myelodysplastic Syndrome (MDS)
- *Acute myeloid leukemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to WHO classification*
- A BCCA “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, AST, ALT, Bilirubin (total and direct), LDH, Albumin, electrolytes, urea, INR, PTT
- On day 1 of each cycle and then weekly: CBC and differential, serum creatinine, electrolytes, GGT, alkaline phosphatase, AST, ALT, LDH, Bilirubin (total and direct), INR, PTT
- 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

**serum creatinine, electrolytes, GGT, alkaline phosphatase, AST, ALT, LDH, Bilirubin (total and direct), INR, PTT

PREMEDICATIONS:

- Prochlorperazine 10mg PO 30 minutes prior to azacitidine
- If above ineffective, then ondansetron 8mg PO 30 minutes prior to azacitidine

TREATMENT:

Drug	Dose**	BCCA Administration Guideline
<u>Standard regimen (preferred)</u>		
Azacitidine	75 mg/m ² /d x 7 days	SC*
	Or	
	50 mg/m ² /d x 7 days	SC*
	Or	
	37.5 mg/m ² /d x 7 days	SC*
<u>Alternative regimen</u> 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	SC*
	Or	
	50 mg/m ² /d x 5 days, no treatment for 2 days†, then 50 mg/m ² /d x 2 days	SC*
	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	SC*

* doses greater than 2.5 mL should be divided into two syringes and administered 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 x 4 cycles and assess:
- If complete response has been achieved, treatment would be continued for another 3 cycles; if partial response or haematological improvement has been achieved (based on peripheral blood counts and bone marrow examination, as previously

defined), treatment would be continued until complete response, progression of disease (increase in marrow blast count) or death.

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
<ul style="list-style-type: none"> 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

Renal dysfunction: Not studied in patients with renal impairment; select dose carefully (excretion is primarily renal; consider dose reduction); monitor closely for toxicity.

- **Dosing adjustment for Renal toxicity:** 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 electrolytes: The manufacturer recommends that 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 BCCA 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.

Date activated: 1 July 2010

Date revised: 1 Mar 2011 (eligibility revised, table added for Tests)

References:

1. Rose BD editor. Drug Information for Azacitidine. UpToDate 16.1 ed. Waltham, Massachusetts: UpToDate®; 2010.
2. Azacitidine Treatment for advanced myelodysplastic syndrome PEC proposal October 6, 2005
3. Krug U, Lubbert M, Bucher T. Maintenance therapy in acute myeloid leukemia revisited: will new agents rekindle an old interest? *Curr Opin Hematol.* 2010;17(2):85-90
4. 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.
5. Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Onc* 2009;27(11):1850-6.