BC Cancer Protocol Summary for Therapy of Acute Myeloid Leukemia Using azaCITIDine and SORAfenib

Protocol Code	*LKAMLAS*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. David Sanford*

ELIGIBILITY:

- Acute myeloid leukemia (AML) with FLT3 ITD mutation
- Refractory to conventional induction and salvage chemotherapy, or relapses within 3 months of salvage therapy
- Eligible for stem cell transplant
- ECOG 0-2

EXCLUSIONS:

- Advanced hepatic tumors
- Significant cardiovascular disease and/or known LVEF less than 50%
- Uncontrolled hypertension

TESTS:

- Baseline: CBC & Diff, creatinine, GGT, alkaline phosphatase, ALT, total bilirubin, LDH, albumin, sodium, potassium, chloride, serum bicarbonate, urea, INR, PTT, total protein, urine analysis, TSH
- 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
- Pre-initial therapy
  - On day 1 of each cycle and then weekly: CBC & Diff, creatinine, sodium, potassium, chloride, serum bicarbonate, GGT, alkaline phosphatase, ALT, LDH, total bilirubin, INR, PTT
  - On Days 3 and 5 of treatment: CBC & Diff (physician responsible to monitor results and advise on supportive treatment)
  - Bone marrow biopsy prior to cycles 2, 3 and 4
  - MUGA scan or echocardiogram if clinically indicated or if history of cardiac problems
- Post-stem cell transplant:
  - Before each cycle: CBC & Diff, creatinine.
  - MUGA scan or echocardiogram if clinically indicated or if history of cardiac problems
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- ondansetron 8 mg PO 30 minutes prior to azaCITIDine
- If required: prochlorperazine 10 mg PO 30 minutes prior to azaCITIDine

SUPPORTIVE MEDICATIONS:

- Moderate risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Pre-initial therapy

Drug	Dose	BC Cancer Administration Guideline
azaCITIDine	75 mg/m^2/d on days 1 to 7	subcutaneous*
SORAfenib	400 mg BID on days 1 to 28	PO

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

- Repeat every 28 days for up to 4 cycles (i.e., 16 weeks)
  - Maximum 4 cycles unless patients are in remission and there is some delay in getting them to transplant
- azaCITIDine may be discontinued after 3 cycles if:
  - ANC less than 1 x10^9/L,
  - Platelets less than 30 x 10^9/L, and
  - No leukemic infiltrate in the marrow
- SORAfenib may be discontinued before 16 weeks if complete response and transplant arranged sooner

Post-stem cell transplant

- 30 to 100 days post-transplant,
- ANC greater than 1.0 x 10^9/L, and
- Platelet greater than 50 x 10^9/L

Drug	Dose	BC Cancer Administration Guideline
SORAfenib	400 mg BID on days 1 to 28	PO

- Repeat every 28 days for up to 1 year

DOSE MODIFICATIONS:

Pre-initial therapy

1. **Hematological**
   Patients with relapsed/refractory AML are cytopenic because of the disease and should receive full dose of both drugs regardless of their ANC during initial therapy unless bone marrow aspirate shows no evidence of leukemia.

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

ANC ($x10^9$/L)	azaCITIDine Dose	SORAfenib Dose
Full dose regardless of ANC if blasts greater than 5% in bone marrow biopsy Bone marrow biopsy prior to cycles 2, 3 and 4	100%	100%
ANC less than 1.0 on day 1 of cycles 2, 3 or 4 and blasts less than 5% in bone marrow	Hold	100%

Post-stem cell transplant

Bone marrow should be in remission and blood count suppression should be avoided.

ANC ($x10^9$/L)	SORAfenib Dose
greater than 1.0 and platelets >50	400 mg BID
ANC below 0.5 prior to next 28 day cycle	400 mg daily
Recurrent ANC below 0.5 after 50% dose reduction	Hold

2. **Renal dysfunction:** see additional information in **Precautions** section

Parameters	azaCITIDine Dose
Unexplained increases in serum creatinine or BUN occur, or decrease in serum bicarbonate to less than 20 mmol/L	Delay next cycle until values reach baseline or normal, then reduce dose by 50% for next treatment course

3. **Cardiac Toxicity:** SORAfenib only.

Asymptomatic

- Continue SORAfenib based on serial LVEFs, if performed for clinical indication

Relationship of LVEF to LLN	**Absolute LVEF decrease from baseline**		
	less than 10%	**10 to 15%**	**greater than 15%**
Within Normal Limits	Continue	Continue	Hold*
1-5% below LLN	Continue	Hold*	Hold*
greater than 5% below LLN	Continue*	Hold*	Hold*

*Re-assess LVEF after 4 weeks

- If criteria for continuation are met, resume SORAfenib
- If 2 consecutive holds or a total of 3 holds occur, discontinue SORAfenib

Symptomatic

- Discontinue SORAfenib if evidence of cardiac dysfunction.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Hepatic dysfunction**:
   - azaCITIDine has not been studied in patients with hepatic impairment. It may be hepatotoxic, with progressive hepatic coma leading to death having been rarely reported in patients with extensive tumor burden, especially those with a baseline albumin less than 30 g/L. It is contraindicated in patients with advanced malignant hepatic tumours.
   - SORAfenib appears safe with mild hepatic impairment (bilirubin less than or equal to 1.5 x upper limit of normal). No data exist with moderate to severe impairment.
3. **Renal dysfunction**:
   - azaCITIDine in combination with chemotherapy have been associated with serum creatinine elevations, renal tubular acidosis, and renal failure.
   - SORAfenib appears safe with mild renal impairment (creatinine less than or equal to 2 x upper limit of normal). No data exist with moderate to severe kidney failure.

4. **Drug interaction**: SORAfenib is predominantly metabolized and excreted through cytochrome P4503A4 in the liver. Potential drug interactions with cytochrome P4503A4 interacting agents must be considered. see also: http://medicine.iupui.edu/flockhart/table.htm
5. **Hypertension:** Patients with hypertension should exercise caution while on SORAfenib. Rigorous treatment of blood pressure is necessary, since SORAfenib can cause a rapid onset of high blood pressure. Temporary suspension of SORAfenib is recommended with severe hypertension (greater than 200 mmHg systolic or greater than 110 mmHg diastolic). Treatment may be resumed once hypertension is controlled (see also http://www.hypertension.ca). For at least the first 2 cycles of treatment, patients should monitor their blood pressure daily (home measurements, GP's office, etc.) and keep a journal of their blood pressure that can be submitted to the physician at the next appointment.
6. **Hepatitis B Reactivation:** See SCHBV protocol for more details.

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. Ravandi F, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood 2013;121:4655-62.
2. Chen YB, et al. Phase 1 trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for Fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. Biol Blood Marrow Transplant 2014;20:2042-8.