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

Protocol Code  
ULKAMLAS

Tumour Group  
Leukemia/BMT

Contact Physician  
Dr. Donna Hogge

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
- A BC Cancer “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment.

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

TESTS:
- Baseline: CBC and differential, platelets, serum creatinine, GGT, alkaline phosphatase, ALT, Bilirubin, LDH, Albumin, sodium, potassium, chloride, serum bicarbonate, urea, INR, PTT, total protein, urine analysis, TSH
- Pre-initial therapy
  - 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
- On Days 3 and 5 of treatment: CBC and differential, platelets (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, differential, creatinine.
  - MUGA scan or echocardiogram if clinically indicated or if history of cardiac problems

Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/terms-of-use.
PREMEDICATIONS:
- prochlorperazine 10 mg PO 30 minutes prior to azaCITIDine
- If above ineffective, then ondansetron 8 mg PO 30 minutes prior to azaCITIDine

TREATMENT:

Pre-initial therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>azaCITIDine</td>
<td>75 mg/m²/d on days 1 to 7  (round dose to nearest 0.1 mg)</td>
<td>SC*</td>
</tr>
<tr>
<td>SORAfenib</td>
<td>400 mg BID on days 1 to 28</td>
<td>PO</td>
</tr>
</tbody>
</table>

* 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 x 10⁹/L,
  - Platelets less than 30 x 10⁹/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 10⁹/L, and
- Platelet greater than 50 x 10⁹/L

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<td>400 mg BID on days 1 to 28</td>
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- 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)

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

**Post-stem cell transplant**

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

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<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>SORAfenib Dose</th>
</tr>
</thead>
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<tr>
<td>greater than 1.0 and platelets &gt;50</td>
<td>400 mg BID</td>
</tr>
<tr>
<td><strong>ANC below 0.5 prior to next 28 day cycle</strong></td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Recurrent ANC below 0.5 after 50% dose reduction</td>
<td>Hold</td>
</tr>
</tbody>
</table>

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

<table>
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<th>Parameters</th>
<th>azaCITIDine Dose</th>
</tr>
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<tbody>
<tr>
<td>Unexplained increases in serum creatinine or BUN occur,</td>
<td>Delay next cycle until values reach baseline or normal, then reduce dose by 50% for next treatment course</td>
</tr>
<tr>
<td>or decrease in serum bicarbonate to less than 20 mmol/L</td>
<td></td>
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</table>
3. **Cardiac Toxicity**: SORAfenib only.

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

<table>
<thead>
<tr>
<th>Relationship of LVEF to LLN</th>
<th>Absolute LVEF decrease from baseline</th>
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<tbody>
<tr>
<td></td>
<td>less than 10%</td>
</tr>
<tr>
<td>Within Normal Limits</td>
<td>Continue</td>
</tr>
<tr>
<td></td>
<td>10 to 15%</td>
</tr>
<tr>
<td>1-5% below LLN</td>
<td>Continue</td>
</tr>
<tr>
<td></td>
<td>greater than 15%</td>
</tr>
<tr>
<td>greater than 5% below LLN</td>
<td>Continue*</td>
</tr>
</tbody>
</table>

*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.

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

**References**: