BCCA Protocol Summary for Palliative Therapy for Renal Cell Carcinoma Using SUNItinib

Protocol Code          UGUSUNI
Tumour Group           Genitourinary
Contact Physician      Dr. C. Kollmannsberger

ELIGIBILITY:
- Advanced renal cell carcinoma with clear cell component
- ECOG performance status less than or equal to 2
- Compassionate Access Program (CAP) approval granted by BCCA
- If patient exhibits poor prognosis criteria, consider Temsirolimus.
  Poor prognosis defined if at least 3 out of 6 risk factors are present (minimum of 3 poor-risk features required):
  - LDH greater than 1.5 X upper limit of normal
  - Hemoglobin less than lower limit of normal
  - Corrected calcium greater than10 mg/dL
  - Time from diagnosis to first treatment less than 1 yr
  - Karnofsky Performance Status 60-70
  - Multiple organ sites of metastasis

EXCLUSIONS:
- Pregnancy
- Significant cardiovascular disease and/or LVEF less than 55
- Uncontrolled hypertension

TESTS:
- Baseline: CBC, differential, platelets, electrolytes, creatinine, total protein, albumin, bilirubin, alkaline phosphatase urine analysis, TSH.
- Before each cycle: CBC, differential and platelets, urine analysis, creatinine, uric acid, ALT, Bilirubin. TSH every other cycle or if clinically indicated.
- MUGA scan or echocardiogram if clinically indicated or if history of cardiac problems

PREMEDICATIONS:
- Antiemetic protocol for low emetogenic chemotherapy protocols (see SCNAUSEA)
TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUNItinib</td>
<td>50 mg once daily for 4 weeks followed by 2 weeks rest*</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>*Each cycle consists of 6 weeks.</td>
<td></td>
</tr>
</tbody>
</table>

Alternatively:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUNItinib</td>
<td>37.5 mg once daily continuously (If patients show rapid progression during the 2 week break)</td>
<td>PO</td>
</tr>
</tbody>
</table>

Dose reduction:
- Dose level -1: 37.5 mg
- Dose level -2: 25 mg

DOSE MODIFICATIONS:

1. Hematological

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose (all drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 1 and Greater than or equal to 75</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Less than 1 or Less than 75</td>
<td>Delay</td>
<td></td>
</tr>
</tbody>
</table>

2. Non-Hematological toxicity:

<table>
<thead>
<tr>
<th>CTC-Grade</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>100%</td>
</tr>
<tr>
<td>3-4 Delay</td>
<td>until less than or equal to grade 1</td>
</tr>
<tr>
<td>Dose reduce by 1 dose level</td>
<td></td>
</tr>
</tbody>
</table>

PRECAUTIONS:

1. Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BCCA Febrile Neutropenia Guidelines.
2. **Cardiac Toxicity:**

Asymptomatic Patients – SUNItinib continuation based on serial LVEFs

<table>
<thead>
<tr>
<th>Relationship of LVEF to LLN</th>
<th>Absolute Decrease Of less than 10%</th>
<th>Absolute Decrease Of 10 -15%</th>
<th>Absolute Decrease Of &gt; 16%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within Normal Limits</td>
<td>Continue</td>
<td>Continue</td>
<td>Hold *</td>
</tr>
<tr>
<td>1-5% below LLN</td>
<td>Continue</td>
<td>Hold *</td>
<td>Hold *</td>
</tr>
<tr>
<td>Greater than or equal to 6% below LLN</td>
<td>Continue *</td>
<td>Hold *</td>
<td>Hold *</td>
</tr>
</tbody>
</table>

LLN = Lower Limit of Normal

- *Repeat LVEF assessment after 4 weeks
- If criteria for continuation are met – resume SUNItinib
- If 2 consecutive holds or a total of 3 holds occur, discontinue SUNItinib

**Symptomatic Patients**

- Symptomatic patients with evidence of cardiac dysfunction should have SUNItinib discontinued

3. **Renal dysfunction:** Only a very small percentage of SUNItinib and its metabolites are excreted by the kidney. SUNItinib appears safe in patients with mild renal impairment (creatinine less than or equal to 2x upper limit of normal). No data exist for SUNItinib in patients with moderate to severe kidney failure.

4. **Hepatic dysfunction:** SUNItinib is mainly metabolized and excreted through the liver. SUNItinib appears safe in patients with mild hepatic impairment (bilirubin less than or equal to 1.5x upper limit of normal). No data exist for SUNItinib in patients with moderate to severe hepatic impairment.

5. **Sunitinib-Induced hypothyroidism:** All patients on SUNItinib should be observed closely for signs and symptoms of thyroid dysfunction (such as fatigue). Patients should have thyroid function laboratory monitoring done (TSH every cycle for cycles 1-4 then every 2-3 months). Patients with minor TSH elevations (up to 20 mU/L), no symptoms and no pre-existing heart disease can be managed with observation. Patients with TSH elevation and symptoms and/or pre-existing heart conditions should be treated as per current recommended guidelines.
Thyroid hormone replacement therapy should be initiated and maintained as follows:

<table>
<thead>
<tr>
<th>Age and Cardiac Disease</th>
<th>Usual Starting Dose of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults under 50 yr with cardiac disease</td>
<td>Levothyroxine 25 – 50 mcg PO daily</td>
</tr>
<tr>
<td>Adults over 50 yr without cardiac disease</td>
<td>Levothyroxine 25 – 50 mcg PO daily</td>
</tr>
<tr>
<td>Adults over 50 yr with cardiac disease</td>
<td>Levothyroxine 12.5 – 25 mcg PO daily</td>
</tr>
</tbody>
</table>

Dose adjustments are needed every 6-8 weeks, based on clinical and laboratory parameters. Close observation of liver function tests and thyroid function is required when patients are receiving both SU11248 and thyroid hormone replacement therapy.

6. **Drug Interaction**: SU11248 is predominantly metabolized and excreted through cytochrome P450 3A4 in the liver. **Potential drug interactions with cytochrome P450 3A4 interacting agents must be considered** (see also: [http://medicine.iupui.edu/flockhart/table.htm](http://medicine.iupui.edu/flockhart/table.htm)).

7. **Hypertension**:
   - Patients with hypertension should exercise caution while on SU11248. Rigorous treatment of blood pressure is necessary, since Sunitinib can cause a rapid onset of high blood pressure. Temporary suspension of sunitinib is recommended for patients with severe hypertension (greater than 200 mmHg systolic or greater than 110 mmHg diastolic). Treatment with sunitinib may be resumed once hypertension is controlled (see also [http://www.hypertension.ca](http://www.hypertension.ca)).
   - It is recommended that for at least the first 2 cycles of treatment patients monitor their blood pressure daily (home measurements, GP’s office, etc.) and keep a journal of their blood pressure measurements that can be submitted to the physician.

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

Date activated: July 1, 2007

Date revised: 1 Mar 2014 (Minor typo corrected).

**References**: