Practice Guideline: Systemic Therapy Summary

First-Line Treatment of Advanced Renal Cell Carcinoma with Oral Sunitinib

(GENU – Sunitinib (MRCC))

Genitourinary Disease Site Group

Effective: February 2008
Required Update: May 2016
Annual Review: May 2015
ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS

There are no relevant conflicts of interest to disclose.
Preface

This document has been prepared by the Winnipeg Regional Health Authority/CancerCare Manitoba (WRHA/CCMB) Oncology Pharmacotherapeutic (P&T) Subcommittee’s Systemic Therapy Summaries Working Group, as a means of disseminating drug information and formulary decisions made by the Subcommittee. The CCMB Provincial Pharmacy Program, Provincial Oncology Drug Program (PODP) and Clinical Practice Guidelines Initiative (CPGI) have contributed to the development of this summary.

Systemic Therapy Summaries (STS) are being developed for drugs/or indications where the P&T Subcommittee, based on scientific data, has accepted clinical benefit. The P&T Subcommittee Chair and the CPGI Lead/Advisory Panel Chair approve all STS documents.

The content of this STS was in large part adapted from the Formulary Addition Request submitted to the P&T Subcommittee by the CCMB Genitourinary (GENU) Disease Site Group (DSG), February 2008. This document will be reviewed, and updated as necessary, once in every twelve-month period; unless emerging evidence from scientific research dictates otherwise.

Purpose

This document is intended as a guide to facilitate the safe and effective clinical use of oral sunitinib in the first-line treatment of advanced renal cell carcinoma.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, nurses, and pharmacists at CancerCare Manitoba, Community Cancer Programs Network (CCPN) sites and WRHA Community Oncology Program sites.

Disclaimer

Use of this document should not preclude the practitioner’s independent clinical judgment, nor should it replace consultation with the oncologist.

It is the responsibility of the practitioner to develop an individualized treatment plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The unique needs and preferences of the patient and the family should always be reflected in the plan of care.

This document is not a comprehensive drug monograph. Practitioners must refer to other sources for complete drug information.
First-Line Treatment of Advanced Renal Cell Carcinoma with Oral Sunitinib

Protocol Code: GENU – Sunitinib (MRCC)

Developed by: Genitourinary Disease Site Group

Date of Presentation to P&T Subcommittee: February 26, 2008

Treatment Recommendation

The Genitourinary DSG recommends oral sunitinib for the first-line treatment of advanced renal cell carcinoma in patients who meet the inclusion criteria (see below).

Treatment Intent

- Non-curative
- Prolongation of overall survival (OS) and progression-free survival (PFS)

Rationale

Most cases of advanced renal cell carcinoma cannot be cured. “Targeted therapy” has become the mainstay of treatment, with both multi-targeted tyrosine kinase inhibitors (TKI) and inhibitors of the mammalian target of rapamycin proving to have clinical activity. Sunitinib remains the TKI with the best evidence to support its use in the first-line treatment of advanced renal cell carcinoma.

Clinical Benefit (Level Ib Evidence see Appendix I)

An international randomized phase III, industry-funded trial compared sunitinib to interferon-α (IFN-α) as a first-line treatment for 750 patients with metastatic renal cell carcinoma. The results of this study showed a significant improvement in median PFS, the primary trial endpoint, of 11 months in the sunitinib arm versus 5 months in the IFN-α arm (hazard ratio [HR], 0.42; p < 0.001). The overall response rate was 31% in the sunitinib arm as compared to 6% in the IFN-α arm.

A trial update from 2009 suggested an OS advantage with sunitinib. The median OS was 26.4 months for sunitinib compared to 21.8 months for the IFN-α group (HR, 0.821; p = 0.051).
Patient Population and Selection Criteria

Inclusion criteria

- Advanced/metastatic renal cell carcinoma of clear-cell histology; AND
- An Eastern Cooperative Oncology Group (ECOG) performance status of $\leq 2$ (see Appendix II); AND
- Low to intermediate risk as defined by Memorial Sloan Kettering Cancer Centre (MSKCC) risk status$^{3,4}$

Exclusion criteria

- Uncontrolled brain metastases; OR
- An ECOG performance status of 3 or 4; OR
- Pregnancy; OR
- Significant cardiovascular disease; OR
- Uncontrolled hypertension

CCMB Formulary Status

1. Formulary definition

- Restricted

2. Adjudication process

- Complete “Restricted Drug Form – GU DSG” (J:\Pharmacy\FORMS)
- Approval required by: Genitourinary DSG Chair or Designate
- Supporting documentation: pathology demonstrating renal cell carcinoma, clear cell histology
- For renewals, imaging results (CT scans) must be submitted

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administrative Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>50 mg once daily for 4 weeks followed by a 2 week rest period (6 week cycle)</td>
<td>Orally, with or without food (12.5 mg, 25 mg or 50 mg capsules)</td>
</tr>
</tbody>
</table>
Clinical Monitoring and Follow-Up Recommendations

**Hematology, chemistry and required tests**

- **Baseline and before each cycle:**
  - Complete blood count (CBC) with differential, serum creatinine, urea, bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), alkaline phosphatase, sodium, potassium, chloride, calcium, albumin, thyroid-stimulating hormone (TSH). Other laboratory tests may be ordered at the physician’s discretion.

**Clinical toxicity assessment**

- **Blood pressure monitoring:**
  - Patients with sunitinib should have their blood pressure monitored weekly for the first cycle and then individualized for subsequent cycles. They should be encouraged to monitor their blood pressure at home, daily, in the first 1-2 cycles, particularly if the blood pressure is elevated at clinic visits.

- **Cardiotoxicity:**
  - If the patient has a known cardiac history or if otherwise clinically indicated, a multigated acquisition scan (MUGA) or echocardiogram (ECG) is to be ordered before initiating sunitinib therapy and then repeated every 4 cycles. Therapy should be discontinued in symptomatic patients with evidence of cardiac dysfunction.
  - In asymptomatic patients in whom baseline left ventricular ejection fractions (LVEF) was established, sunitinib continuation is based on serial LVEF monitoring (see Dose Modifications).
  - Perform ECG at baseline, at the end of the first cycle, and if any of the following occur (specifically looking at QTc interval):
    - Sunitinib dose escalation for any reason
    - Sunitinib dose reduction due to QTc interval prolongation
    - Significant electrolyte changes, vomiting and/or diarrhea, addition of a CYP 3A4 inhibitor

- **Thyrotoxicity:**
  - Patients treated with sunitinib should be observed for signs and symptoms of thyroid dysfunction (e.g., fatigue, weight gain, fluid retention).
  - TSH monitoring should be done for cycles 1-4 and repeated every 2-3 months thereafter in all patients. Minor TSH elevation (up to 20 mU/L) with no symptoms can be observed, provided the patient has no pre-existing heart disease.
  - Thyroid hormone replacement therapy should be initiated in patients with TSH elevation and symptoms and/or pre-existing heart conditions.

**Recommended starting doses:**

- Adults under 50 years with cardiac disease – levothyroxine 25 – 50 mcg PO daily
- Adults over 50 years with cardiac disease – levothyroxine 12.5 – 25 mcg PO daily
- Adults without cardiac disease – levothyroxine 25 – 50 mcg PO daily
- Adults over 50 years without cardiac disease – levothyroxine 25 – 50 mcg PO daily

Patients receiving sunitinib and thyroid replacement therapy require close observation of liver and thyroid function. Dose adjustments should be done every 6-8 weeks based on clinical and laboratory findings.

**Assessment of treatment response**

- Clinical follow-up with CT scans (or appropriate diagnostic imaging) should be repeated every 2 cycles; CT scan should be performed during the 4th week of every even cycle, *while patient is still on treatment*
- If imaging shows clinically relevant progressive disease, sunitinib therapy should be discontinued
## Common or Clinically Important Adverse Events*
(Refer to individual drug monographs for full details of adverse events)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Hypertension (all grades) was reported as an adverse event in 16.6% of metastatic renal cell carcinoma patients receiving sunitinib. Grade 3 or 4 hypertension was observed in 4.1% of patients. Since sunitinib can cause rapid onset of hypertension, it is recommended that patients be monitored closely, and treated with standard antihypertensive therapy according to clinical symptoms. Non-dihydropyridine calcium channel blockers such as diltiazem and verapamil should be avoided, as they are known CYP 3A4 inhibitors.</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Sunitinib’s active substance is yellow. Skin and hair discoloration is a common treatment-related adverse event that occurs in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with this drug.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Abnormal TSH concentrations have been documented in 62% of patients. Persistent primary hypothyroidism developed in 36% of patients after a range of 12 to 94 weeks of sunitinib therapy. Eighteen percent of patients taking sunitinib for 36 weeks developed hypothyroidism, 29% of patients taking sunitinib for 1 year were affected, and 90% of patients treated for more than 96 weeks developed increased TSH levels. The incidence of hypothyroidism appears to increase progressively with the duration of therapy.</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>Decreased LVEF has been reported in up to 12% of patients treated with sunitinib. However, Grade 3 to 4 (symptomatic) ventricular dysfunction was seen in only 2% of patients in the phase III clinical trial, and symptoms reversed after dose modification or discontinuation of sunitinib.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Emetogenic potential of regimen = low (10-30%)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea, mucositis/stomatitis, sore tongue, nausea, dysgeusia (impaired sense of taste) – most Grade 1 or 2</td>
</tr>
<tr>
<td>Other common adverse</td>
<td>Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) 12-14%; fatigue, bleeding events and tumour hemorrhage (most Grade 1 or 2)</td>
</tr>
<tr>
<td>effects</td>
<td></td>
</tr>
</tbody>
</table>

* See Appendix III CTCAE v.4.0
## Dose Modifications*

* Note: Medical Oncologists at CancerCare Manitoba will typically alter the schedule rather than the dose for these patients. Please consult the prescribing physician.

<table>
<thead>
<tr>
<th>Dose Level Reduction</th>
<th>Dose</th>
<th>Hepatic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; dose level reduction: 37.5 mg</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; dose level reduction: 25 mg</td>
<td>Sunitinib is mainly metabolized and excreted through the liver. No data exist for sunitinib in patients with moderate to severe hepatic impairment, however this drug appears to be safe for patients with mild hepatic impairment (bilirubin ≤ 1.5 x upper limit of normal [ULN])</td>
</tr>
</tbody>
</table>

| Renal dysfunction | One study has indicated that sunitinib is safe to use in patients with significant renal failure. However, treatment was more frequently discontinued due to adverse events and the duration of therapy was significantly shorter in these patients |

### Hematological toxicity

<table>
<thead>
<tr>
<th>Day 1 Blood Counts</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≥ 1.0 x 10⁹/L and platelets ≥ 75 x 10⁹/L</td>
<td>100%</td>
</tr>
<tr>
<td>ANC &lt; 1.0 x 10⁹/L or platelets &lt; 75 x 10⁹/L</td>
<td>Delay</td>
</tr>
</tbody>
</table>

### Cardiac toxicity*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue at the same dose level</td>
</tr>
</tbody>
</table>
| 2     | Continue at the same dose level, except in the event of:  
• Asymptomatic decrease of LVEF by an absolute value of 20% and to below lower limit of normal |
<table>
<thead>
<tr>
<th>Grade</th>
<th>Non-hematological toxicity requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>Non-urgent ventricular paroxysmal dysrhythmia requiring intervention. Withhold dose until toxicity is ≤ Grade 1, then reduce dose by 1 level and resume treatment.</td>
</tr>
<tr>
<td>3</td>
<td>Withhold dose until toxicity is ≤ Grade 1, or has returned to baseline, then reduce the dose by 1 level and resume treatment.</td>
</tr>
<tr>
<td>4</td>
<td>Discontinue sunitinib.</td>
</tr>
</tbody>
</table>

* (Table adapted from Kollmannsberger MD, et al. 2007)⁷

<table>
<thead>
<tr>
<th>Grade</th>
<th>Disease flare during two-week break requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consider continuous dosing: 37.5 mg once daily on Days 1 – 42 with no break.</td>
</tr>
</tbody>
</table>
### Drug Interactions<sup>9,10</sup>

| Drug-drug interactions | **CYP 3A4 inhibitors** – may increase sunitinib concentrations.  
**CYP 3A4 inducers** – may decrease sunitinib concentrations.  
**Drugs which prolong QT/QTc interval** – concomitant use of sunitinib with other QT/QTc prolonging drugs is discouraged. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-food interactions</td>
<td><strong>Grapefruit juice</strong> – has CYP 3A4 inhibitory activity. Patients who consume grapefruit juice while taking sunitinib will have decreased sunitinib metabolism and increased plasma concentrations.</td>
</tr>
<tr>
<td>Drug-herb interactions</td>
<td><strong>St. John’s wort</strong> – may increase sunitinib metabolism and therefore decrease sunitinib plasma concentrations.</td>
</tr>
</tbody>
</table>
References


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Appendix I

### Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence obtained from at least one other type of well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

Appendix II

ECOG Performance Status Scale

<table>
<thead>
<tr>
<th></th>
<th>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70-80)</td>
</tr>
<tr>
<td>1</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about greater than or equal to 50% of waking hours (Karnofsky 50-60)</td>
</tr>
<tr>
<td>2</td>
<td>Capable of only limited self-care, confined to bed or chair greater than or equal to 50% of waking hours (Karnofsky 30-40)</td>
</tr>
<tr>
<td>3</td>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)</td>
</tr>
</tbody>
</table>

## Appendix III

### Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

**Publish Date: 18 May 2009**

#### Grades

Grade refers to the severity of the AE. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>

A semi-colon indicates ‘or’ within the description of the grade.
A single dash (-) indicates a grade is not available.
Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

**Grade 5:** Grade 5 (Death) is not appropriate for some AEs and therefore is not an option

**Activities of Daily Living (ADL):**

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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