Practice Guideline: Systemic Therapy Summary

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

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CancerCare Manitoba
Practice Guideline: Systemic Therapy Summary

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Protocol Code: GENU-Sunitinib (MRCC)

Introduction

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 clinical benefit has been accepted by the P&T Subcommittee, based on scientific data. All STS documents are approved by the P&T Subcommittee Chair and the CPGI Lead/Advisory Panel Chair.

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) Systemic Therapy Group, 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 use of the practitioner’s independent clinical judgement, 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 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 Sunitinib (Oral)
Protocol Code: GENU-Sunitinib (MRCC)
Developed by: Genitourinary (GENU) Systemic Therapy Group
Date of Presentation to P&T Subcommittee: February 2008

Treatment Recommendation
Sunitinib is recommended for the first-line treatment of advanced renal cell carcinoma in patients who meet the inclusion criteria described below.

Treatment Intent
- Non-curative
- Prolongation of progression-free survival; probable prolongation of overall survival

Rationale
Most cases of advanced renal cell carcinoma cannot be cured. Interferon alfa and interleukin-2 have been the main treatments for metastatic renal cell carcinoma. Cytokines have limited efficacy and substantial toxicity, and no other treatment options have been available for this disease.

Clinical Benefit (Level 1 Evidence see Appendix I)
An international phase III randomised, industry funded trial compared sunitinib to interferon alfa as first-line treatment of 750 patients with metastatic renal cell carcinoma. The results showed a significant improvement in median progression-free survival, the primary trial endpoint, of 11 months in the sunitinib arm versus 5 months in the interferon arm (hazard ratio 0.42 and P<0.001). The overall response rate was 31% in the sunitinib group as compared to 6% in the interferon group.

A recent trial update, published August 2009, suggested an overall survival advantage with sunitinib. The median overall survival was 26.4 months for sunitinib compared to 21.8 months for the interferon group (hazard ratio=0.821; P=0.051).

Patient Population and Selection Criteria

Inclusion criteria (February 08)
- Clear cell histology component
- An ECOG performance status score of 2 or lower (see Appendix II)
- Low to intermediate risk as defined by Memorial Sloan Kettering Cancer Centre risk status (see Appendix III)

Pharmacare criteria (April 08)
- For the treatment of metastatic renal cell carcinoma (MRCC) in patients with favorable to intermediate-risk disease (Part 3 EDS)

Exclusion criteria (February 08)
- Uncontrolled brain metastases
- ECOG performance status of 3 or 4
- Pregnancy
- Significant cardiovascular disease and/or reduced LVEF
- Uncontrolled hypertension
CCMB Formulary Status

1. Formulary definition
   - Pharmacare Part 3*
   - P&T Subcommittee Drug Approval Process Step 1b**

* Approval will be granted by Pharmacare if specific criteria for use are met.
** Clinical benefit accepted by the P&T Subcommittee based on scientific evidence. Recommended for review by the Economic Evaluation and Budget Impact Subcommittee.

2. Adjudication process
   - Request form to use: Sunitinib Request Form (J:\Forms\Pharmacy)
   - Approval required by: GENU- Systemic Therapy Group Chair or delegate

Following treatment approval by the Chair of the GENU Systemic Therapy Group, the request form is faxed to Manitoba Health for Pharmacare Part 3 approval.* The initial approval will be granted for 3 months (two 6-week cycles); approval beyond 3 months will require a renewal request.
* Patient is responsible for payment of Pharmacare deductible.

### Treatment Regimen – Sunitinib

1 cycle = 6 weeks (planned treatment until progression or intolerable toxicity)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>sunitinib</td>
<td>50 mg orally 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, 50 mg capsule strength</td>
</tr>
</tbody>
</table>
Clinical Monitoring and Follow-Up Recommendations

Hematology and chemistry laboratory tests

Baseline and before each cycle: CBC with differential, serum creatinine, urea, bilirubin, AST, ALT, LDH, GGT, alkaline phosphatase, sodium, potassium, chloride, calcium, albumin, TSH. Other laboratory tests may be ordered at the physician’s discretion.

Clinical toxicity assessment

Blood pressure monitoring: Patients treated with sunitinib should have their blood pressure monitored weekly for the first cycle and then individualized for subsequent cycles.

Cardiotoxicity: MUGA scan or echocardiogram (Echo) 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, sunitinib continuation is based on serial left ventricular ejection fractions (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 CYP3A4 inhibitor

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 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>Adverse Event</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 MRCC 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 left ventricular ejection fraction (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>
</tbody>
</table>
| Gastrointestinal toxicities | Emetogenic potential of regimen\(^6,7\) = Low (10-30%)  
Diarrhea, mucositis/stomatitis, sore tongue, nausea, dysgeusia (impaired sense of taste) – most grade 1 or 2. |
| Other common adverse effects | Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) 12-14%; fatigue, bleeding events and tumour hemorrhage (most grade 1 or 2). |

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

### Hepatic dysfunction

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 less than or equal to 1.5 times the upper limit of normal).

### Renal dysfunction

No data exist in patients with moderate to severe kidney failure. Use of sunitinib appears to be safe in patients with mild renal impairment (serum creatinine less than or equal to 2 times the upper limit of normal).

### Hematological toxicity

<table>
<thead>
<tr>
<th>Blood Counts</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC greater than or equal to $1.0 \times 10^9$/L and Platelets greater than or equal to $75 \times 10^9$/L</td>
<td>100%</td>
</tr>
<tr>
<td>ANC less than $1.0 \times 10^9$/L or Platelets less than $75 \times 10^9$/L</td>
<td>Delay</td>
</tr>
</tbody>
</table>

### Cardiac toxicity*

* Table adapted from Kollmannsberger MD, et al. (2007) 6

<table>
<thead>
<tr>
<th>Grade</th>
<th>Sunitinib 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  
|       | • non-urgent ventricular paroxysmal dysrhythmia requiring intervention  
|       | With-hold dose until toxicity is grade 1 or less, then reduce dose by 1 level and resume treatment |
| 3     | With-hold dose until toxicity is grade 1 or less, or has returned to baseline, then reduce the dose by 1 level and resume treatment |
| 4     | Discontinue sunitinib |

### Non-Hematological toxicities

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 2</td>
<td>100%</td>
</tr>
</tbody>
</table>
| 3 - 4     | Delay until grade 1 or lower  
|           | Dose reduce by 1 dose level:  
|           | 1st dose level reduction: 37.5 mg  
|           | 2nd dose level reduction: 25 mg |

### Disease flare during two-week break

Consider continuous dosing  
37.5 mg once daily on Days 1 – 42 with no break
# Drug Interactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-food interactions</td>
<td>Grapefruit juice has CYP 3A4 inhibitory activity. Patients who consume grapefruit juice while taking sunitinib will have decreased sunitinib metabolism and increased plasma concentrations.</td>
</tr>
</tbody>
</table>
| Drug-drug interactions | CYP 3A4 inhibitors: Inhibitors of CYP 3A4 may increase sunitinib concentrations.  
CYP 3A4 inducers: Inducers of CYP 3A4 may decrease sunitinib concentrations.  
For a complete list of CYP 3A4 substrates, inhibitors, and inducers, please see: [http://medicine.iupui.edu/flockhart/table.htm](http://medicine.iupui.edu/flockhart/table.htm) |
| Drugs which prolong QT/QTc interval | The concomitant use of sunitinib with another QT/QTc prolonging drug is discouraged. |
| Drug-herb interactions | Patients should avoid taking St. John’s wort while on sunitinib because it may increase sunitinib metabolism and therefore decrease sunitinib plasma concentrations. |
References


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Ms. Kimberly Watkinson, BSc (Pharm), Provincial Oncology Drug Program

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Approved By (2010)

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Chair, WRHA/CCMB Oncology Pharmacotherapeutic Subcommittee

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Lead and Advisory Panel Chair, CCMB Clinical Practice Guidelines Initiative

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The Provincial Oncology Clinical Practice Guidelines Initiative
## 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>

British Committee for Standards in Haematology 2007

[http://www.bcshguidelines.com](http://www.bcshguidelines.com)
### Appendix II

**ECOG Performance Status Scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</td>
</tr>
<tr>
<td>1</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>2</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>3</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>4</td>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)</td>
</tr>
</tbody>
</table>

### Memorial Sloan Kettering Cancer Centre

**Prognostic Risk Categories for Advanced Renal Cell Carcinoma**

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Poor</td>
<td>3 or more</td>
</tr>
</tbody>
</table>

Risk factors associated with shorter survival:

- low hemoglobin
- high corrected calcium
- high LDH
- poor performance status
- interval of less than 1 year from diagnosis to treatment

Appendix IV

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
Publish Date: 28 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:

Grade 1  Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2  Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3  Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4  Life-threatening consequences; urgent intervention indicated.

Grade 5  Death related to AE.

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.
