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## Evidence-Based Series 3-8-4

# The Use of Inhibitors of Angiogenesis in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer

*S. Hotte, T. Waldron, G. Bjarnason, M. Jewett, M. MacKenzie, R. Segal, E. Winquist,  
and the Genitourinary Cancer Disease Site Group*

A Quality Initiative of the  
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 30, 2009

An assessment conducted in December 2012 placed Evidence-based Series (EBS) 3-8-4 **IN REVIEW**. This means that it is undergoing a review for currency and relevance. The Genitourinary Disease Site Group (DSG) has determined that it is still appropriate for this document to continue to be available while this updating process unfolds.

Evidence-based Series (EBS) 3-8-4, consists of three sections:

Section 1: Guideline Recommendations

Section 2: Evidentiary Base

Section 3: EBS Development Methods and External Review Process

and is available on the CCO Web site (<http://www.cancercare.on.ca>)

PEBC Genitourinary Cancer DSG page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genito-ebs/>

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: [ccopgi@mcmaster.ca](mailto:ccopgi@mcmaster.ca)

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## Evidence-Based Series 3-8-4: Section 1

# The Use of Inhibitors of Angiogenesis in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Guideline Recommendations

*S. Hotte, T. Waldron, G. Bjarnason, M. Jewett, M. MacKenzie, R. Segal, E. Winquist,  
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### QUESTION

In adult patients with inoperable locally advanced or metastatic renal cell cancer (RCC):

1. Does treatment with inhibitors of angiogenesis improve overall (OS) and/or progression-free survival (PFS)? Secondary outcomes of interest include quality of life (QOL), objective tumour response rate, clinical response rate, and adverse effects.
2. Is a combination of inhibitors of angiogenesis better than any single-agent angiogenesis inhibitor?
3. Does sequential administration of a second inhibitor of angiogenesis offer additional benefit to patients?

### RECOMMENDATIONS

Immunotherapy with or without cytoreductive nephrectomy has been the standard of care in patients with inoperable locally advanced or metastatic RCC. There is now evidence of important clinical benefit for agents that inhibit angiogenesis in this patient population.

- Sunitinib is recommended as first-line therapy for appropriate patients with favourable<sup>1</sup>-to intermediate-risk<sup>2</sup> disease based on a 58% reduction in the risk of disease progression or death.

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Memorial Sloan-Kettering Cancer Center (MSKCC) (1) risk factors: low performance status, high lactate dehydrogenase, low serum hemoglobin, high corrected calcium, and time from diagnosis to treatment of less than 12 months. Please refer to Appendix 1 of Section 2: Evidentiary Base for a more detailed explanation of these risk factors.

<sup>1</sup> Favourable-risk: 0 risk factors present

<sup>2</sup> Intermediate-risk: 1 or 2 risk factors present

- The dose used in the trial of sunitinib was 50mg daily by mouth for four weeks, followed by two weeks off drug, in repeated six-week cycles.
- Bevacizumab combined with interferon-alpha (IFN-a) reduces the risk of disease progression or death by 35% as first-line therapy in patients with favourable<sup>1</sup>- and intermediate-risk<sup>2</sup> disease. This benefit appears potentially inferior to the benefit associated with sunitinib, and in light of the associated toxicities of IFN-a therapy, bevacizumab combined with IFN-a is not recommended. Current data do not support the use of single-agent bevacizumab, and therefore bevacizumab alone is also not recommended.
- Temsirolimus is recommended as first-line therapy for patients with poor-risk disease<sup>3</sup>, based on a 27% reduction in the risk of death.
  - The dose used in the trial of temsirolimus was 25mg intravenously, once per week.
- Everolimus is recommended as second- or third-line therapy in patients previously treated with sunitinib, sorafenib, or both, based on a 70% reduction in the risk of disease progression.
  - The dose used in the trial of everolimus was 10 mg daily by mouth given in four-week cycles.
- Sorafenib should be considered a treatment option in patients who progress following initial immunotherapy, based on a 56% reduction in the risk of disease progression or death reported with second-line therapy in patients with favourable<sup>1</sup>- to intermediate-risk<sup>2</sup> disease previously treated with immunotherapy.
  - The dose used in the trial of sorafenib was 400mg by mouth twice daily, continuously.

#### QUALIFYING STATEMENTS

- Although not statistically significant and confounded by the crossover of patients from control to experimental therapy, the current evidence for OS benefit with first-line sunitinib and second-line sorafenib is compelling and consistent with the PFS benefit.
- Cytoreductive nephrectomy is associated with a survival benefit in RCC (see Evidence-based Series #3-8-3), but the biological basis for this effect is uncertain. Very few patients in the trials of sunitinib, sorafenib, everolimus, and bevacizumab had not had their primary kidney tumour excised. Therefore, in addition to uncertainty about the role of cytoreductive nephrectomy in patients receiving these drugs, there is also uncertainty about the generalizability of the benefits of these drugs to patients whose primary tumours remain in situ.
- These agents have toxicities that require monitoring by physicians experienced in their use.
- Currently, there is insufficient evidence to recommend combination or sequential use of these agents.
- Immunotherapy has limited activity and important toxicities; therefore, inhibitors of angiogenesis are preferred.
- Evidence from key randomized trials is continuing to mature, and this clinical practice guideline will be updated as additional data become available.

#### KEY EVIDENCE

- Eleven randomized controlled trials (RCTs) satisfied the eligibility criteria; however, because outcome data were unavailable or incomplete for two trials, nine of the 11

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<sup>3</sup> Poor risk defined as a modification of Mekhail et al risk criteria (2); includes the risk factors listed above and number of metastatic sites (but excludes prior radiotherapy); poor risk= >2 risk factors present.

eligible trials form the evidence base for this review. All nine trials addressed Question 1. Four trials were published in abstract form. The number of eligible patients per trial ranged from 116 to 903 and totalled 5,053 patients.

- Six different inhibitors of angiogenesis were studied: bevacizumab (three trials), sorafenib (two trials), sunitinib (one trial), temsirolimus (one trial), everolimus (one trial), and thalidomide (one trial). These agents were examined as first-line and second- or third-line treatment in six and three trials, respectively.
- First-line treatment:
  - *Bevacizumab* - two large RCTs (n=1381) reported significantly longer PFS with bevacizumab combined with IFN- $\alpha$  compared to IFN- $\alpha$ , either alone or with placebo. Pooling the PFS data from the two trials in a meta-analysis produced a hazard ratio (HR) of 0.65 (95% confidence interval [CI], 0.58-0.74;  $p<0.00001$ ), which represents a 35% decrease in the risk of progression or death with combination therapy. Final OS results are expected when the trial data mature. Combination therapy was associated with more grade 3/4 adverse effects and treatment discontinuations; however, in both treatment arms the most frequently reported grade 3/4 effects were IFN- $\alpha$  associated toxicities. Eight and seven patient deaths due to adverse effects were reported with combination and control therapy, respectively; three of those deaths were possibly attributable to treatment with bevacizumab.
  - *Sunitinib* - one large trial (n=750) reported significantly longer PFS with sunitinib compared with IFN- $\alpha$  (median, 45 months versus [vs.] 11 months; HR=0.42; 95% CI, 0.33 to 0.52;  $p<0.001$ ). OS was also longer with sunitinib, but this benefit was of borderline statistical significance. Median survival times were 26.4 months and 21.8 months for sunitinib and IFN- $\alpha$ , respectively. Sunitinib was associated with a greater frequency of the following grade 3/4 adverse effects: neutropenia, leucopenia, thrombocytopenia, diarrhea, vomiting, hypertension, and hand-foot syndrome. Health-related QOL was better with sunitinib ( $p<0.001$ ). Less than 10% of patients were poor risk in this trial.
  - *Temsirolimus* - one large trial (n=626) that included only poor-risk RCC patients reported longer OS with single-agent temsirolimus compared to IFN- $\alpha$  (median, 10.9 months vs. 7.3 months; HR=0.73; 95% CI, 0.58 to 0.92;  $p=0.008$ ). No survival benefit was observed with temsirolimus/IFN- $\alpha$  combined treatment. Median PFS was also longer in patients treated with temsirolimus, either alone or combined with IFN- $\alpha$ . Temsirolimus-based regimens were associated with significantly more grade 3/4 anemia, neutropenia, and thrombocytopenia.
  - *Sorafenib* - one phase II trial (n=189) compared sorafenib to IFN- $\alpha$ . No difference in PFS was observed between treatment arms. The incidence of grade 3/4 adverse effects was similar across the treatment arms; hand-foot skin reactions, rash, and diarrhea were more common with sorafenib.
  - *Thalidomide* - one trial (n=342) comparing combination thalidomide/IFN- $\alpha$  to IFN- $\alpha$  alone reported no differences in OS and a one month improvement in PFS with combination treatment (3.8 months vs. 2.8 months;  $p=0.04$ ).
- Second-line treatment:
  - *Sorafenib* - the largest trial (n=903), comparing sorafenib to placebo in patients who had failed prior immunotherapy, reported sorafenib significantly prolonged PFS over placebo (median, 5.5 months vs. 2.8 months; HR=0.44; 95% CI, 0.35 to 0.55;  $p<0.001$ ). OS, the primary endpoint, was analyzed just prior to treatment crossover after 6.6 months of follow-up; sorafenib was associated with a 28% reduction in the risk of death compared to placebo (HR=0.72; 95% CI, 0.54 to 0.94;  $p=0.02$ ). However, this result did not reach the threshold set for statistical significance ( $p<0.0005$ ). Grade

3/4 hypertension ( $p<0.001$ ) and hand-foot skin reactions ( $p<0.001$ ), and cardiac ischemia or infarction (3% vs. 1%) were more common with sorafenib. Serious adverse events leading to hospitalization or death occurred in 34% of patients receiving sorafenib and 24% of patients receiving placebo ( $p<0.01$ ). No differences in overall QOL were detected between the two arms, although sorafenib improved the following symptoms: cough, fever, worry that condition will worsen, shortness of breath, and ability to enjoy life. Poor-risk patients were not included in this trial.

- *Bevacizumab* - one randomized phase II trial ( $n=116$ ) reported longer time-to-disease progression with low-dose bevacizumab (median, 4.8 months;  $HR=2.55$ ;  $p<0.001$ ) and a marginal benefit with high-dose bevacizumab (median, 3 months;  $HR=1.26$ ;  $p=0.053$ ) compared to placebo (median, 2.5 months). No differences in OS were observed between treatment arms.
- Second- or third-line treatment:
  - *Everolimus* - one phase III trial ( $n=410$ ) compared everolimus to placebo in patients who had progressed on either sunitinib or sorafenib or both. PFS was significantly prolonged with everolimus compared with placebo ( $HR=0.30$ ; 95% CI, 0.22 to 0.40;  $p<0.0001$ ). No significant difference in OS was observed. However, 81% of patients in the placebo control arm crossed over to everolimus therapy at the time of disease progression. Compared with placebo, everolimus was associated with higher rates of grade 3/4 stomatitis, infections and non-infectious pneumonitis, and caused more adverse effects leading to treatment discontinuations and dose reductions. No differences in health-related QOL were observed between trial arms.

#### RELATED GUIDELINES

- Evidence-based Series #3-8-1: *The Use of Interferon-alpha for the Treatment of Patients with Locally Advanced or Metastatic Renal Cell Cancer (in progress).*
- Evidence-based Series #3-8-2: *Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer.*
- Evidence-based Series #3-8-3: *The Role of Cytoablative Nephrectomy in the Management of Patients Treated with Immunotherapy for Metastatic Renal Cell Cancer.*

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#### *Contact Information*

For further information about this report, please contact:

**Dr. Sebastien Hotte, Co-Chair, Genitourinary Cancer DSG**

Juravinski Cancer Centre, Hamilton, ON

Phone: 905-387-9495 x64602 Fax: 905-575-6326 E-mail: [Sebastien.Hotte@jcc.hhsc.ca](mailto:Sebastien.Hotte@jcc.hhsc.ca)

**Dr. Eric Winquist**

London Health Sciences Centre, London, ON

Phone: 519-685-8600 x53346 Fax: 519-685-8624 Email: [eric.winqvist@lhsc.on.ca](mailto:eric.winqvist@lhsc.on.ca)

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: [ccopgi@mcmaster.ca](mailto:ccopgi@mcmaster.ca)

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