Management of advanced kidney cancer: Canadian Kidney Cancer Forum 2013 Consensus Update

Canadian Kidney Cancer Forum 2013

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This is the fourth report from the Kidney Cancer Research Network of Canada (KCRNC) with an update from the fourth Canadian Kidney Cancer Forum held in January 2013 in Toronto, Ontario, Canada.[1-3]

Kidney cancer, predominantly renal cell carcinoma (RCC), is the most lethal genitourinary malignancy and kills more than 1700 Canadians a year.[4] The overall incidence is increasing by 2% per year for unknown reasons; most new cases are small renal masses. Targeted systemic therapies, which have been integrated into clinical practice with evolving experience, have been available for more than 7 years. Preservation of kidney function with widespread adoption of partial nephrectomy is a focus of treatment of early stage disease. These and other advances have revolutionized care and stimulated research. There are several guidelines in Canada that address various aspects of RCC patient care.[2,3,5,6]

Three previous forums were held in 2008, 2009 and 2011. As before, this 2013 meeting was small, by invitation and attended by survivors, caregivers, expert clinicians and researchers in kidney cancer field. The attendees included representatives of Kidney Cancer Canada.[7]

During the conference, prior consensus statements were reviewed and updated using the same process. This report is an update of the advanced disease management component of the consensus published in 2011.[3] The Forum again addressed the following: (1) strategies for kidney cancer control in Canada, which includes the now operational Canadian Kidney Cancer Information System (CKCis); (2) the development of a coordinated approach to validating the proposed genetic testing guidelines for patients and families at risk for kidney cancer; (3) the fostering of an increased awareness of cancer survivorship issues, especially the development of a survivorship care plan; and (4) the continuation of the quality process to validate the now defined quality indicators for the management of kidney cancer. Meeting participants also discussed the delivery models of genetic testing and counselling for patients with kidney cancer and the need for the availability of services for patients with potentially hereditary cancers. Finally, a number of new research initiatives for the "personalized medicine" care of kidney cancer were proposed. These will be the subject of future reports. This consensus statement pertains to the management of advanced disease. A separate document discussing early disease, including diagnosis and surgical management, will be published as a separate document.

Management of locally advanced kidney cancer

Neoadjuvant therapy

There is no indication for neoadjuvant therapy prior to planned surgical resection outside the context of a clinical trial.

If patients are felt to be surgically resectable at diagnosis, they should proceed immediately to surgery. Routine use of neoadjuvant therapies is not indicated at this time. The final results of clinical trials with adjuvant and neoadjuvant anti-angiogenic agents (vascular endothelial growth factor receptor tyrosine kinase inhibitors [VEGFr TKI], VEGF antibodies or mammalian target of rapamycin [mTOR] inhibitors) will not be available for several more years. Some patients deemed inoperable at diagnosis may have a dramatic response to targeted therapy and if there is any question that they may have converted to an operable state, they should be re-evaluated by a urologist.

Adjuvant therapy

There is no indication for adjuvant therapy after surgical resection, unless in the context of a clinical trial.

Adjuvant therapy with cytokines does not improve overall survival after nephrectomy.[8] The results of several clinical trials with adjuvant anti-angiogenic agents (VEGFr TKI, VEGF antibodies or mTOR inhibitors) will not be available for several more years. Patients with high-risk tumours, who have undergone complete resection, should be encouraged to participate in clinical trials whenever possible.

Advanced (metastatic) kidney cancer

Enrolling patients in well-designed clinical trials should always be the first option for patients with advanced or metastatic RCC.

First-line therapy

- **Targeted therapy is the preferred treatment (Table 1).**
- **Observation can also be considered, for some patients with slow growing asymptomatic disease.**
- **High-dose interleukin-2 (IL-2) can be considered in highly selected patients.**

The field of systemic therapy is evolving quickly and the recommendations made in this document reflect the available evidence at the time the consensus conference participants reached their conclusions. As new data become available, the treatment options will invariably change.

RCC is a heterogeneous disease and there are several prognostic factors that may help clinicians risk stratify their patients. These include clinical factors, such as patient performance status, and laboratory parameters. The first of these prognostic scores was published by Motzer and colleagues and was used to define entry criteria or to stratify for patient enrolment in clinical trials.[9] It is for this reason that the treatment recommendations in Table 1 and the text below differ based on patient risk. This prognostication system was developed in the cytokine era. In the targeted therapy era, Heng and colleagues have published a similar, but not identical, risk stratification score which is applicable to patients receiving therapy today.[10]

Based on phase III clinical trial data, **sunitinib** produces higher response rates, improved quality of life (QOL) and a longer progression-free survival (PFS) than interferon-alfa in patients with metastatic clear cell RCC (mRCC).[11] Subsequent survival analysis showed that patients treated with sunitinib had a longer overall survival (OS) than those treated with interferon.[12] In addition, population-based studies from British Columbia and Alberta have shown an almost doubling of OS of mRCC since the introduction of sunitinib and sorafenib.[13,14] The dose and schedule of sunitinib should be optimized for each patient to derive the most benefit. This may require adjustments from the standard 4-week on/2-week off dosing schedule.[15] Based on phase III data**, pazopanib** produces an improvement in PFS compared to placebo in both cytokine naïve and refractory patients.[16] As first-line therapy, pazopanib has also been shown to be non-inferior to sunitinib with respect to PFS in the phase III COMPARZ (COMParing the efficacy, sAfety and toleRability of paZopanib vs. sunitinib) clinical trial (abstract information only).[17] Another VEGFr TKI**, tivozanib**, has demonstrated superior PFS compared to sorafenib in a phase III clinical trial of patients with clear cell RCC who were either treatment naïve or had no more than 1 prior line of therapy (excluding VEGFr TKI or mTOR inhibitors).[18]

Based on phase III data, **temsirolimus** produces an improvement in PFS and OS in poorer risk patients than interferon alone or combined temsirolimus and inter-

Table 1. Treatment recommendations

Setting	Patients	Therapy (Level 1 evidence)	Other options (Less than Level 1 evidence)
Untreated	Good or intermediate risk	Sunitinib Bevacizumab+IFN* Pazopanib Tivozanib**	HD IL-2 Sorafenib Observation
	Poor risk	Temsirolimus	Sunitinib
Second-line	Cytokine refractory	Sorafenib Pazopanib Tivozanib** Axitinib	Sunitinib, bevacizumab+IFN*
	Prior VEGF targeted therapy	Everolimus Axitinib	Targeted therapy not previously used
	Prior mTOR		VEGFr TKI
Third line* **	Any		Targeted therapy not previously used

IFN: interferon; HD IL-2: high-dose interleukin-2; VEGF: vascular endothelial growth factor; VEGFr TKI: VEGF receptor-tyrosine kinase inhibitor; mTOR: mammalian target of rapamycin.
*The combination of bevacizumab + IFN has not been approved in Canada but is approved in the United States and Europe. **At the present time, tivozanib has not received Health Canada approval. ***At the present time, there is no Health Canada approved third line systemic therapy.

feron.[19] Poorer risk was defined by at least 3/6 of the following criteria: Karnofsky Performance Scale (KPS) 60-70; ↑Ca++; ↓hemoglobin; ↑lactate dehydrogenase; <1 year from nephrectomy to treatment; or multiple metastatic sites. Where drug access is limited, **everolimus**, if available, would be a reasonable alternative.[20] In patients with intolerance to sunitinib, pazopanib, temsirolimus or sorafenib remain good options.[21]

There is phase III data demonstrating that combined bevacizumab and interferon improves PFS over interferon alone.[22,23] At this time, there has not been an application submitted regarding bevacizumab for use in kidney cancer in Canada; therefore, it is not an option for Canadian patients.

The meeting attendees determined that an initial period of **observation** is reasonable in select patients, given that no systemic therapies are currently considered curative, that all available treatments can have side effects, and that some patients may experience an indolent clinical course with slowly growing asymptomatic metastases.

No phase III studies on the use of **IL-2** have shown an improvement in survival, and thus it is not considered a standard of care, but may be in highly selected patients. Based on phase II data, however, a very select group of patients may be considered for high-dose IL-2.[24] High-dose IL-2 must be delivered in specialized and experienced centres and ideally in the context of a clinical trial or investigational setting. Low-dose IL-2 should not be given.[25,26]

In patients with metastatic or advanced RCC with non-clear cell histology, enrolment in clinical trials should be encouraged. Other options include: **sunitinib**, based on subgroup analyses from the Expanded Access trial showing safety and activity; **sorafenib**, based on subgroup analyses from the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial showing safety and activity; and **temsirolimus**, based on subgroup analysis of phase III data.[27-30] In patients with advanced or metastatic sarcomatoid or poorly differentiated RCC, options include: **sunitinib**, based on prospective, non-randomized data from the Expanded Access Program; **sorafenib**, based on prospective, non-randomized data from the ARCC expanded access trial; **chemotherapy**, based on phase II data utilizing agents, such as 5-fluorouracil, gemcitabine, doxorubicin, and combinations of these showing activity; and **temsirolimus,** based on subgroup analysis from the pivotal phase III trial in which these patients were eligible.[27-29,31]

When prescribing systemic therapy for advanced or metastatic RCC, several key factors must be taken into account. An oncology specialist should prescribe therapy; this person should know about acute and long-term toxicities, drug interactions, and monitoring treatment and response. Patients should be managed in a multidisciplinary environment with adequate resources, including nursing care, dietary care and pharmacy support. Patients must be evaluated frequently to ensure toxicities are recognized and managed appropriately. Patients and caregivers should be provided with information concerning potential side effects and their prevention, treatment and management.

Progression on or intolerance to cytokines

Based on phase III data, **sorafenib** improved PFS compared to best supportive care alone in previously treated patients who had received IL-2 or interferon.[32] OS data were confounded by crossover, but reached significance when censored for crossover. **Pazopanib** has also been studied in this patient population and improves PFS compared to placebo.[16] **Axitinib** has also shown an improvement in PFS compared to sorafenib in this population. In the AXIS (axitinib vs. sorafenib in advanced RCC) trial, about one-third of the subjects had received first-line cytokines at the time of study enrolment and PFS was prolonged with the use of axitinib.[33] Similarly, **tivozanib** has shown superior PFS compared to sorafenib in this population.[18] **Sunitinib** is an alternate treatment. Based on two phase II trials, **sunitinib** produced significant response rates and increased PFS compared to historical controls.[34]

Progression after first-line targeted therapy

- **Clinical trials in this population should be supported as the optimal sequence of therapies is unknown.**
- **Switch to another targeted agent (Table 1).**

Based on phase III data, **everolimus** (oral mTOR inhibitor) produced a significantly longer PFS than placebo, with an acceptable toxicity profile in patients who had failed sunitinib or sorafenib (or both).[35] Should everolimus not be available, temsirolimus should not routinely be substituted given its inferior outcomes when compared to sorafenib in this patient population as shown in the INTORSECT study.[36]

Based on the phase III AXIS trial**, axitinib** has shown improved PFS compared to sorafenib as second-line therapy in patients progressing after first-line therapy with sunitinib and would be another reasonable second-line option.[33]

At this time, there is no evidence to help determine which second-line therapy after VEGFr TKI is superior, thus everolimus or axitinib would be suitable choices.

In patients with advanced or metastatic RCC post-sunitinib or sorafenib failure, other options include: **switching to another VEGFrTKI** (e.g., from sunitinib to sorafenib or from sorafenib to sunitinib) based on emerging data showing activity with sequential therapy.[37] The role of interferon post-targeted therapy is unclear.

For patients whose first-line therapy was an mTOR inhibitor, there is no Level I evidence to guide treatment decisions in the second-line setting. The use of a VEGFr TKI in this

setting is a reasonable option, however, this recommendation is made based on less than Level I evidence.[38]

Currently, Health Canada has not approved any agents in the third-line setting. However, there is data to support use of targeted therapies in this setting. In the RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily) trial of everolimus versus placebo, 25% of subjects randomized had received 2 VEGFR TKI therapies prior to enrolment and there was a significant improvement in PFS in the group receiving everolimus.[20] Thus, everolimus would be a reasonable choice for patients in this setting.

Role of cytoreductive nephrectomy

Cytoreductive nephrectomy should be considered in appropriately selected patients presenting with mRCC.

Recommendations for this section are based on Level I evidence in patients treated with interferon. Appropriately selected patients for cytoreductive nephrectomy (CN) include: patients with a primary tumour amenable to surgical extirpation and a low risk of perioperative morbidity, patients with good performance status (ECOG 0 or 1), and patients without evidence of brain metastases.[25,37-38] It is important to ensure that patients undergoing CN meet these criteria to maximize benefit and that there is no concern about rapid disease progression that would require immediately starting systemic therapy.

At this point, there are no randomized data on the use of CN in the era of targeted therapy. Decisions are based on extrapolation from (1) the Interferon data; (2) retrospective North American data showing improved outcomes in patients with CN prior to targeted therapy; (3) the fact that most patients (>90%) enrolled in the VEGFr TKI phase III clinical trials had a prior CN; and (4) and clinical judgment.[9,20,32,39-41] Prospective studies on the benefit of CN are required and several trials are currently underway. Canadian investigators are participating in the EORTC 30073 SURTIME trial.

In patients who do not undergo upfront CN, but have a good response to VEGFrTKI or targeted therapy, limited metastatic disease and good performance status, CN may be considered in the course of their treatment.

Role of metastatectomy

In select patients with limited sites of metastatic disease and clinical stability resection of the metastatic disease may be reasonable.

There are no randomized trials demonstrating the benefit for metastatectomy in RCC. However, among patients with metachronous metastases after nephrectomy, about one-third are eligible for metastatectomy; several large cohorts report a 50% 5-year survival following complete resection of metastases.[37,42,43] Based on available observational data, patients most likely to benefit from metastatectomy are those diagnosed with metastases over 2 years following nephrectomy; those with isolated metastases; and those with favourable metastatic locations. A period of observation is reasonable to confirm that the metastatic disease is indolent.

Role of radiation therapy

Radiation therapy may be considered to control bleeding and pain from the primary tumour, to palliate symptoms from metastases and to stabilize brain metastases.

RCC is not a radio-resistant tumour and many patients can achieve palliation of symptoms related to their cancer through radiation therapy. New radiation techniques, such as stereotactic radiation therapy, may improve outcomes compared to traditional external beam radiation therapy; ongoing trials are in progress.[44] Clinical trials involving radiation should be supported.

Role of bone targeted agents for patients with skeletal metastases

About one-third of patients with metastatic RCC will develop bone metastases as part of their disease,[45] which can lead to skeletal-related events (SRE). Currently available bone-modifying agents have been shown to reduce SREs in this population. In a phase III trial of zoledronic acid (ZA) versus placebo, a subset analysis of 74 RCC patients showed that administration of ZA compared to placebo resulted in a significant decrease in SREs in the ZA group (44% compared to 74% in placebo).[46] Specific results from this subgroup have been published separately. There was a significant reduction of SREs in the group receiving ZA 4 mg intravenously monthly compared to placebo.[47] Therefore, monthly administration of ZA is a reasonable option. Careful monitoring of renal function is required. Patients receiving bisphosphonates are at risk of hypocalcemia, so calcium and vitamin D supplements are recommended. However, since paraneoplastic hypercalcemia can also occur in RCC, monitoring of serum calcium levels is important. Patients starting any bone targeted therapy should ensure they have had a thorough dental exam prior to starting therapy and ongoing monitoring for osteonecrosis of the jaw (ONJ).

Denosumab is a receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor. In a phase III trial of denosumab versus ZA to treat malignancy with bone metastases (excluding breast or prostate cancer patients), a subset of patients enrolled in this trial had metastatic RCC. This trial demonstrated non-inferiority for denosumab compared to

ZA in terms of SRE reduction for the group overall, although no subgroup analysis for RCC patients has been conducted.[48] In light of this, denosumab could also be considered a reasonable option for this population of patients. Calcium and vitamin D supplementation and careful serum calcium monitoring are also required for patients receiving denosumab, as well as a thorough dental examination and monitoring for ONJ.

Summary

Advanced RCC has seen many advances in treatment in the last several years, with the introduction of many targeted therapies into the treatment paradigm. Therapy should be individualized based on patient risk and each agent selected should be optimized in terms of dose and schedule to obtain maximal benefit. The optimal sequence of agents is still unclear and the subject of ongoing clinical trials. Multidisciplinary care is paramount in maximizing patient benefit. However, despite recent advances, many patients still die of metastatic RCC and ongoing support of clinical trials to further our knowledge in the field is essential.

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