First-line treatment options in metastatic renal cell cancer

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Abstract

The introduction of targeted therapy a decade ago revolutionized the treatment of metastatic renal cell carcinoma (mRCC). The current standard of care focuses on the inhibition of angiogenesis through the targeting of the vascular endothelial growth factor receptor (VEGFR) and the mammalian target of rapamycin (mTOR). Currently recommended first-line treatments in Canada include sunitinib, pazopanib, and temsirolimus. With the heterogeneity of mRCC disease, the choice of treatment is driven largely by prognostic factors.

Introduction

Kidney cancer, most commonly renal cell carcinoma (RCC), is the sixth most common malignancy among Canadian men and the eleventh most common malignancy among Canadian women, with an estimated 6200 new cases diagnosed each year.[1] With a lack of specific screening tests to diagnose RCC, up to 30% of all patients will present with metastatic RCC (mRCC) at diagnosis.[2] RCC is largely resistant to cytotoxic chemotherapy and radiotherapy;[3-5] therefore, the arrival of targeted systemic therapies over a decade ago transformed the landscape of RCC treatment.

Current first-line treatments for RCC in Canada include the anti-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) sunitinib and pazopanib, and the mammalian target of rapamycin (mTOR) inhibitor temsirolimus (Table 1). Because RCC is a heterogeneous disease, the choice of treatment is driven largely by prognostic factors.[6,7] The classic Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) prognostic model[6] categorizes patients into three prognostic groups — favourable, intermediate, or poor — based on the presence of risk factors, including anemia, hypercalcemia, Karnofsky performance status less than 80%, time from diagnosis to treatment of less than one year, serum lactate dehydrogenase more than 1.5 times the upper limit of normal, and absence of prior nephrectomy. However, this model was developed before the era of targeted therapies. More recently, Heng and colleagues validated a similar risk stratification model that is applicable to patients receiving targeted therapy.[7] For patients with good or intermediate prognosis, sunitinib and pazopanib are recommended for the first-line treatment of advanced RCC of predominantly clear-cell histology by the National Comprehensive Cancer Network (NCCN)[8] and the European Society for Medical Oncology (ESMO)[9] guidelines, as well as the Canadian Kidney Cancer Forum.[10] For patients with poor prognosis, temsirolimus is recommended. Sunitinib and pazopanib have also shown to be of benefit in the treatment of poor-prognosis patients.[11] The ESMO and NCCN guidelines also recommend the combination of bevacizumab and interferon for the first-line treatment of patients with good or intermediate prognosis; however, this combination has not been approved in Canada. The majority of recommendations relate to RCC with clear-cell histology, as it is largely this common histological subtype that has been studied in clinical trials. Patients with metastatic or advanced RCC with non-clear-cell histology should be enrolled in clinical trials when possible.[10] Other options include sunitinib, sorafenib and temsirolimus. For patients with advanced or metastatic sarcomatoid or poorly differentiated RCC, options include sunitinib, sorafenib, chemotherapy, and temsirolimus.[10]

Sunitinib

Sunitinib was approved by Health Canada in 2006 for the treatment of clear-cell mRCC after failure of cytokine-based therapy or in patients who are considered likely to be intolerant of cytokine-based therapy.[12] The pivotal phase 3 clinical trial of sunitinib in the first-line setting showed higher response rates, improved quality of life, and prolonged progression-free survival (PFS) and overall survival (OS) compared with interferon-alfa (IFN-alfa) in patients with clear-cell mRCC (Fig. 1).[13,14] The recommended starting dose for sunitinib is one 50 mg oral dose taken once daily for four weeks, followed by two weeks off.[12] However, nearly half of patients require a dose reduction.[13] The optimal dose and schedule for sunitinib have been explored in a prospective phase 2 study examining individualized dosing of sunitinib aimed at keeping toxicities to Grade 2 or lower.[15] Patients were started on sunitinib 50 mg/day for four weeks, with a

Table 1. Summary of agents approved in Canada for the first-line treatment of advanced renal cell carcinoma

Agent	Brand name	Targets	Most common treatment-related adverse effects
Sunitinib[12]	Sutent® (Pfizer)	VEGFR, PDGFR, RAF	Fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discolouration, dry skin, hair colour changes, altered taste, anorexia, bleeding
Pazopanib[25]	Votrient® (Novartis)	VEGFR, FLT3, c-KIT, PDGFR	Diarrhea, nausea, vomiting, abdominal pain, hypertension, fatigue, asthenia, hair colour changes, anorexia, headache, liver toxicity
Temsirolimus[26]	Torisel® (Pfizer)	mTOR, HIF-1, HIF-2, VEGF	Rash, asthenia, mucositis, nausea, edema, anorexia

FLT3: Fms-like tyrosine kinase receptor-3; mTOR: mammalian target of rapamycin; PDGFR: platelet-derived growth factor receptor; VEGFR: vascular endothelial growth factor receptor.

one-week break. Those with higher than Grade 2 toxicities were treated according to an altered schedule of two weeks on/one week off to maximize dose intensity while minimizing toxicity. Patients with no toxicities had their dose increased to 62.5 mg and then 75 mg on a two-week-on/one-week-off schedule, resulting in an objective response rate of 50.6% and a disease control rate of 89.2%. A prospective confirmatory trial is underway to explore whether individual sunitinib scheduling based on toxicity might improve survival.[16] Data from Canadian Kidney Cancer information system (CKCis) evaluating outcomes and toxicities with first-line sunitinib vs. pazopanib in patients with clear-cell metastatic RCC was recently presented at ESMO 2016 and showed that the median OS was longer for sunitinib compared to pazopanib (31.7 months vs. 20.6 months; adjusted HR 0.60; p=0.028); there was no significant difference in TTF (11.0 months for sunitinib vs. 8.4 months for pazopanib; p=0.130; adjusted HR 0.87 [95% CI 0.59–1.28]).[17]

Pazopanib

Pazopanib became available in Canada in 2010 based on results of a phase 3 clinical trial showing a significant PFS benefit in patients with mRCC of good performance status (Eastern Cooperative Oncology Group [ECOG] Grade 0–1) (Fig. 2).[18] However, OS and health-related quality of life (HRQOL) benefits were not demonstrated with pazopanib vs. placebo in the pivotal phase 3 trial. More recently, the phase 3 COMPARZ trial[19] demonstrated non-inferiority of pazopanib compared with sunitinib with respect to PFS, and a similar OS as sunitinib. Toxicities were different; sunitinib was associated with a higher incidence of fatigue, hand-foot syndrome, and thrombocytopenia, while pazopanib was associated with increased levels of alanine aminotransferase and liver toxicity. In the randomized, crossover PISCES trial evaluating patient preferences for pazopanib or sunitinib, 70% of patients preferred pazopanib over sunitinib, 22% preferred sunitinib, and 8% had no preference.[20] HRQOL and adverse events were key factors influencing this preference.

Temsirolimus

For patients with a poor prognosis, temsirolimus is currently the only drug that has demonstrated efficacy in the first-line setting in a phase 3 study.[21] Patients with previously untreated, poor-prognosis mRCC were randomly assigned to temsirolimus 25 mg IV weekly, IFN-alfa 18×10⁶ IU three times weekly, or a combination of temsirolimus and IFN-alfa three times weekly. Treatment with temsirolimus alone

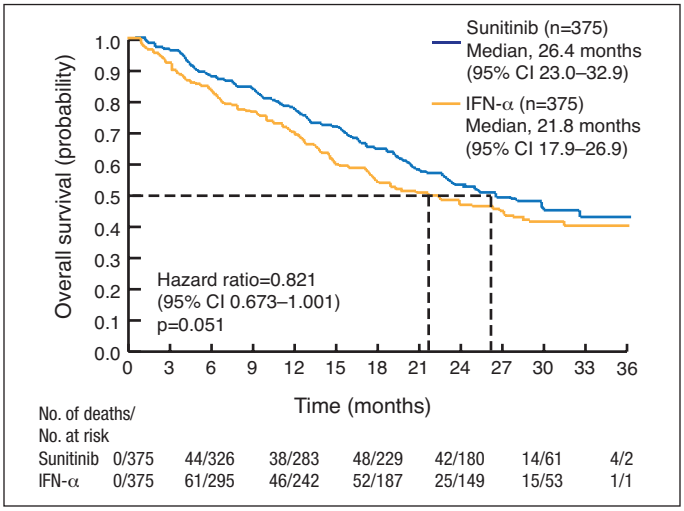

Fig. 1. Overall survival of 750 treatment-naive patients with metastatic renal cell carcinoma treated with sunitinib or interferon-alfa.[14] CI: confidence interval; IFN: interferon.

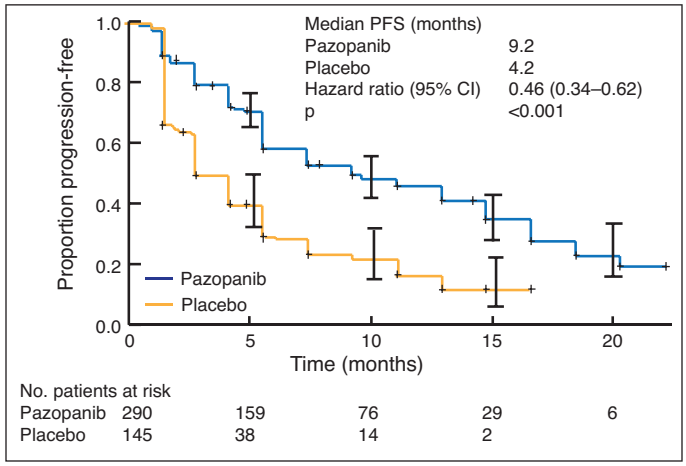

Fig. 2. Progression-free survival of 435 patients with advanced or metastatic renal cell carcinoma treated with pazopanib or placebo.[18] CI: confidence interval; PFS: progression-free survival.

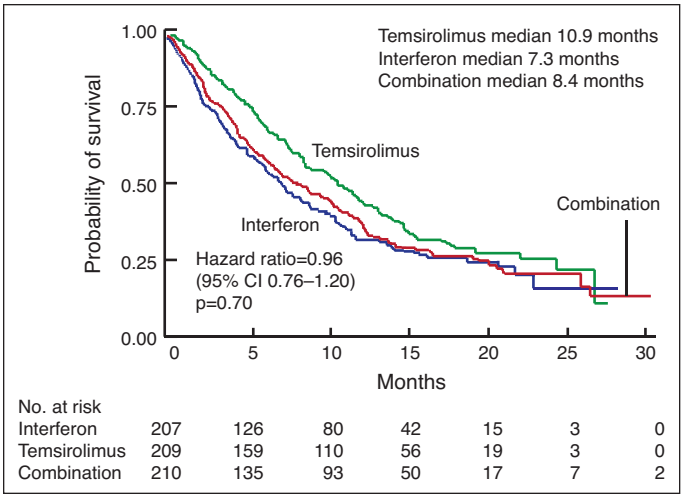

Fig. 3. Overall survival in a phase 3 study of 626 patients with previously untreated, poor-prognosis metastatic renal cell carcinoma randomly assigned to temsirolimus 25 mg IV weekly, interferon-alfa 18×10^6 IU three times weekly, or a combination of temsirolimus and interferon-alfa three times weekly.[21]
CI: confidence interval.

resulted in a longer OS compared with IFN-alfa (Fig. 3). In this study, poor risk was determined by a Karnofsky performance score of 60 or more (on a scale of 0–100, where higher scores indicate a better performance).

Other first-line options not available in Canada

Phase 3 data have shown that the combination of bevacizumab plus interferon improves PFS compared with IFN alone in patients with previously untreated mRCC.[22,23] However, this combination therapy has not been submitted for approval for the treatment of mRCC in Canada and is, therefore, not an option for Canadian patients.

The recent randomized, phase 2 CABOSUN trial compared cabozantinib and sunitinib in patients with previously untreated advanced RCC with intermediate- or poor-risk disease.[24] Both cabozantinib and sunitinib are TKIs; however, whereas sunitinib is a VEGFR inhibitor, cabozantinib inhibits a broader range of enzymes, including VEGFR, MET, and AXL. PFS and response rates were improved with cabozantinib compared with sunitinib in patients with untreated mRCC compared with sunitinib.[24]

Conclusion

Current first-line treatment options for patients with mRCC include single agents that target the VEGF or mTOR pathways. For patients with a good or intermediate prognosis, the VEGF inhibitors sunitinib and pazopanib are currently used in the first-line setting, while the mTOR inhibitor temsirolimus is reserved for patients with a poor prognosis. Sunitinib and pazopanib also have efficacy in poor-prognosis patients. The use of prognostic factors is, therefore, critical to the selection of optimal therapy for patients with mRCC.

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