Renal cell carcinoma (RCC) is a common malignancy. Many patients already have locally advanced or metastatic disease when first diagnosed. In addition, patients with localized disease are at significant risk of progression despite surgical treatment. Chemotherapy is generally ineffective, while immunotherapy benefits only a small minority of patients and is associated with significant toxicity. The von Hippel-Lindau (VHL) gene is commonly mutated in RCC. Understanding the interaction of the VHL gene and cellular signalling pathways affecting angiogenesis has led to the development of targeted therapies. Three agents — bevacizumab, sorafenib and sunitinib — have demonstrated activity against the vascular endothelial growth factor (VEGF) pathway and improved progression-free survival in clinical trials of patients with advanced disease. The U.S. Federal Drug Administration (FDA) and Health Canada have approved sorafenib and sunitinib for the treatment of advanced RCC. A fourth targeted agent, temsirolimus, also downregulates the VEGF pathway through inhibition of mTOR kinase. This is the only targeted agent to have shown improved overall survival in a clinical trial of patients with advanced RCC, however the study was restricted to a poor-risk population. Research is ongoing to assess the role of targeted agents in combinations with chemotherapy, immunotherapy and other targeted therapies.

Renal cell carcinoma is the seventh most common cancer in Canada, with an estimated 4600 new cases diagnosed in 2006. Approximately 95% of cases are sporadic (i.e. not hereditary). Risk factors include smoking, obesity, hypertension, acquired cystic kidney disease and exposure to trichloroethylene.

A THERAPEUTIC CHALLENGE

Conventional clear cell carcinoma is the most common RCC histology, representing 70% of cases (Table 1). Historically, RCC was known as the “internist’s tumour” because of its diverse presentation with features such as erythrocytosis and hypercalcaemia. Less than 10% of patients present with the classic symptom triad of flank pain, hematuria and palpable abdominal mass. With the advent of modern imaging, over half of new cases are now found incidentally. Unfortunately, 25% of patients with RCC present with locally advanced or metastatic disease, and one-third of those treated initially by nephrectomy with curative intent develop recurrent disease. Median survival for metastatic RCC is approximately 13 months, but this average encompasses a wide spectrum of outcomes as the rate of growth is quite variable between patients. To better prognosticate survival, Motzer et al at Memorial Sloan Kettering Cancer Center performed a retrospective review of 670 patients with advanced RCC who were undergoing therapy.4

### Table 1. Malignant renal tumour classification2

<table>
<thead>
<tr>
<th>histology</th>
<th>frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>conventional (clear cell) carcinoma</td>
<td>70%</td>
</tr>
<tr>
<td>papillary (chromophil)</td>
<td>10% to 15%</td>
</tr>
<tr>
<td>chromophobe</td>
<td>5%</td>
</tr>
<tr>
<td>collecting duct</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>unclassified</td>
<td>4% to 5%</td>
</tr>
</tbody>
</table>
They defined the 5 key prognostic clinical factors that can be used to stratify this population into high, intermediate and poor prognosis (Table 2).

**SURGERY**
Surgery has a well-established role in advanced RCC. Palliative nephrectomy may be beneficial in patients with severe flank pain or gross hematuria. Cytoreductive nephrectomy in combination with interferon-alpha (INFα) offers an approximate 5- to 6-month survival advantage over INFα alone in selected patients with good performance status. In addition, metastectomy can be curative in patients with isolated metastases and slow-growing disease, with 5-year overall survival rates of up to 35% to 50%.6

**SYSTEMIC THERAPY**
Chemotherapy
Chemotherapeutic agents have little activity in RCC. Many malignant renal cells possess the multidrug resistance gene. In a systematic review of Phase II trials of chemotherapeutic agents evaluated from 1990 through 1998,7 response rates ranged from 0% to 21% with the majority of response rates less than 10%. Recently, promising Phase II results have been reported for the combination of gemcitabine and infusional fluorouracil with a response rate of up to 30%.8

Immunotherapy
Until recently, immunotherapy was the mainstay of treatment for advanced RCC. This was based on pathologic findings of T cell infiltrates in tumour specimens, chronic stable disease (SD) and spontaneous regressions attributed to immune surveillance. In a Cochrane review of immunotherapy in RCC, INFα had a low response rate of 12.5% and a modest survival advantage of 3.8 months, with an odds ratio for death at 1 year of 0.56 (95% CI 0.40–0.77).9 Meanwhile, high-dose interleukin-2 (IL2) has a slightly better response rate of approximately 20% and offers durable complete responses (CR) in 5% to 7% of patients but no overall survival benefit. Toxicities for both therapies are significant.

Another form of immunotherapy under investigation with promising results is nonmyeloablative allogeneic peripheral blood stem cell transplantation, which uses the “graft vs tumour” effect. An initial case series of 19 patients showed efficacy with 3 CR and 7 partial responses (PR).10 Responses were delayed, however: median time to regression of metastases was 129 days, and treatment-related morbidity and mortality was significant, with 2 toxic deaths. Twelve subsequent reports by various groups have shown mixed results, with response rates from 0% to 57%, and trials are ongoing.11

**TARGETED THERAPIES**
Hereditary forms of RCC provide valuable insight into the pathophysiology of the disease. In particular, the gene mutation on chromosome 3p seen in the rare autosomal dominant von Hippel-Lindau (VHL) syndrome (features include retinal angiomas, hemangioblastomas of the central nervous system, pheochromocytomas and clear cell RCC) has yielded important information about RCC. This gene is also mutated in up to 60% of sporadic clear cell RCC cases. The VHL gene is a tumour suppressor gene associated with the regulation of hypoxia-inducible factors (HIF), which are involved in angiogenesis. The VHL gene protein product promotes the destruction of HIFα via ubiquitination, that is, attachment of one or more ubiquitin proteins to HIFα, triggering a signal for subsequent degradation by intracellular proteasomes. Mutation of the VHL gene and loss of the gene product results in excess HIFα, which is involved in angiogenesis (VEGF) and platelet-derived growth factor (PDGF), as shown in Figure 1, page 12.12-14

**Bevacizumab**
The first agent to successfully target the angiogenesis pathway in RCC was the humanized monoclonal antibody to VEGF, bevacizumab. Yang et al randomized 116 patients with clear cell histology (the majority previously treated with IL2) to a placebo-controlled 3-arm Phase II trial of 2 dose

---

**TABLE 2. Memorial Sloan Kettering Cancer Center prognostic criteria for metastatic RCCa**

<table>
<thead>
<tr>
<th>factor</th>
<th>cutoff indicating more risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky performance status</td>
<td>&lt; 80%</td>
</tr>
<tr>
<td>serum lactate dehydrogenase</td>
<td>&gt; 1.5 times the upper limit of normal</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>&lt; lower limit of normal</td>
</tr>
<tr>
<td>corrected serum calcium</td>
<td>&gt; upper limit of normal</td>
</tr>
<tr>
<td>prior nephrectomy</td>
<td>absence</td>
</tr>
</tbody>
</table>

**risk groups**

<table>
<thead>
<tr>
<th>prognosis</th>
<th>frequency</th>
<th>median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>favourable (0 risk factors)</td>
<td>25%</td>
<td>20 months</td>
</tr>
<tr>
<td>intermediate (1–2 risk factors)</td>
<td>53%</td>
<td>10 months</td>
</tr>
<tr>
<td>poor (3 or more risk factors)</td>
<td>22%</td>
<td>4 months</td>
</tr>
</tbody>
</table>

---

(©2007 Parkhurst, publisher of Oncology Exchange. All rights reserved)
levels of bevacizumab. The high-dose arm showed a modest response rate with only 4 PR in 39 patients but no improvement in overall survival. However, it did demonstrate a statistically significant 2.3-month improvement in time to progression (4.8 vs 2.5 months, p < 0.001). Toxicities included malaise, hypertension and proteinuria. This proof of concept result supported further research of agents targeting this pathway. Two Phase III randomized controlled trials are currently underway comparing high-dose bevacizumab + INFα to INFα alone as first-line treatment.

**Sorafenib**

Sorafenib is an oral multikinase inhibitor targeting both the Raf serine/threonine and VEGF/PDGF receptor kinases. A Phase III randomized placebo-controlled trial of second-line sorafenib after failure of immunotherapy enrolled 903 patients with clear cell histology and good or intermediate risk profiles. The primary endpoint was overall survival, however, interim analysis detected a statistically significant improvement in progression-free survival (PFS) of 5.8 months for sorafenib vs 2.8 months for placebo (p < 0.001). The data monitoring committee decided to halt the study and allow patients to cross from the placebo to the sorafenib arm. Objective response rate was 10% percent (1 CR, 43 PR) with an increased proportion of stable disease of 74% for sorafenib vs 53% for placebo. Six months after crossover, median overall survival of patients receiving sorafenib was 19.3 vs 15.9 months for those on placebo (HR 0.77, 95% CI 0.63–0.95, p = 0.02), but this result did not reach the prespecified statistical significance. Based on PFS data, sorafenib received both FDA and Health Canada approval for the treatment of advanced RCC. Results from first-line Phase III studies of sorafenib are pending.

**Sunitinib**

Sunitinib malate, another oral VEGF/PDGF receptor kinase inhibitor, was studied in 2 Phase II uncontrolled studies in the second-line setting. A total of 168 patients demonstrated objective response rates of 40% to 44% and PFS of 8.3–8.7 months. Based on this preliminary data, sunitinib received both FDA and Health Canada approval as first-line treatment.

The advent of targeted therapies has led to a paradigm shift in the management of RCC. Dr. Michael Atkins of the Dana-Farber/Harvard Cancer Center presented a possible evidence-based treatment algorithm at a plenary session at
As CO, shown in Figure 2. INFα no longer plays a role as a single agent in the first-line therapy of RCC, having been replaced by targeted therapies. Despite their promising activity, however, resistance to targeted therapies emerges in the majority of patients and thus IL2, with its small proportion of durable CR, still has a place in carefully selected patients in first-line treatment. The optimal dosing, sequence and combination of agents in locally advanced and metastatic RCC has yet to be determined and the algorithm will continue to evolve.

Targeted therapies may also play a role in earlier disease, for example as adjuvant therapy for micrometastatic disease after curative nephrectomy. An Eastern Cooperative Oncology Group (ECOG) 3-arm, randomized, double-blind 1-year trial of adjuvant sorafenib vs sunitinib vs placebo in patients after nephrectomy is currently underway. The study will enroll over 1300 patients with the goal of a 25% relative improvement in disease free survival (DFS) from 5.8 to 7.7 years.

Quantifying tumour response in the assessment of targeted therapies in RCC has been challenging. Traditional RECIST (response evaluation criteria in solid tumors) rules are often inadequate, as these agents tend to be cytostatic and result more in disease stabilization as opposed to producing dramatic tumour shrinkage. Radiologically, cell death may manifest as necrosis and/or cavitation of tumours without changing the overall dimensions of measurable lesions. An increased proportion of stable disease has led to the term “clinical benefit,” defined as CR + PR + SD, and the use of waterfall plots to display tumour measurement changes in all patients, not only those meeting response criteria (a waterfall plot is an ordinal graphic display of individual response rates from worst to best along a single axis).

Clinical trials of targeted therapies have also forced a re-evaluation of the definition of clinically relevant measures of activity. When objective response rates are less reflective of drug activity, endpoints such as PFS become more significant. For example, sorafenib was able to improve PFS despite a poor response rate. Improvements in PFS signify a longer period of time in which patients are potentially free of symptoms and the complications associated with tumour growth.

Overall survival is arguably the most important endpoint of interest to clinicians and other decision-makers in oncology trials. Sunitinib and sorafenib have both demonstrated improvements in PFS but not in overall survival. DFS and PFS have previously been correlated to improved overall survival in other tumour sites such as breast and colon cancer. A correlation of PFS to overall survival has yet to be documented in trials of targeted therapy in RCC, probably due to confounding from control patient cross-over to targeted therapy. Upcoming clinical trials need to further explore quality of life endpoints, particularly in the incurable setting of advanced RCC.

The RCC population has provided an ideal model to develop targeted therapies. Many oncologists treating metastatic RCC will continue to agree that this disease remains the “internist’s tumour.” This is because, in addition to its diverse clinical presentations, metastatic RCC now demands clinical skills required to optimally use targeted agents, assess a patient’s response to them, and manage their novel side effect profiles.

References


Disclosure

Dr. Camli reports recently serving on an advisory board for Pfizer. Dr. Reaume reports serving on advisory boards for Wyeth and Pfizer, speakers’ bureau of Pfizer, and receiving an unrestricted educational grant from Bayer.

FIGURE 2. Suggested algorithm for renal cell cancer therapy based on Phase III data

<table>
<thead>
<tr>
<th>setting</th>
<th>therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>first-line therapy</td>
<td>good and intermediate risk</td>
</tr>
<tr>
<td>poor risk</td>
<td>temsirolimus</td>
</tr>
<tr>
<td>second-line therapy</td>
<td>failure of cytokine therapies</td>
</tr>
<tr>
<td></td>
<td>sorafenib</td>
</tr>
<tr>
<td></td>
<td>failure of VEGFR or mTOR inhibitor therapies</td>
</tr>
</tbody>
</table>

©2007 Parkhurst, publisher of Oncology Exchange. All rights reserved.