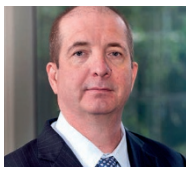
PERSPECTIVE



What next for treatment?

We need to focus on five main areas to make real progress in the treatment of kidney cancer, says **Robert J. Motzer**.

The past ten years have brought unprecedented progress in the treatment of advanced kidney cancer. Before 2005, most patients who presented with distant metastases survived for less than one year. Kidney cancer (renal cell carcinoma) is highly resistant to chemotherapy, and at that time there was only one approved treatment — high-dose interleukin-2. But this required inpatient administration to manage the severe toxicity, and benefited few patients. A breakthrough in treatment options came with the discovery that clear-cell renal cell carcinoma, which is the predominant subtype, is characterized by a mutation in the *VHL* gene that drives angiogenesis. This led to the study, and the subsequent regulatory approval, of sunitinib[1,2] and six other antiangiogenic drugs (pazopanib, axitinib, sorafenib, bevacizumab, cabozantanib and lenvatinib). These drugs, along with two mTOR inhibitors and the immunotherapy drug nivolumab have become the mainstay of treatment[2]. The three newest drugs were approved only within the past year. By using the targeted drugs in sequence and switching drugs as the tumour progresses, most patients are living much longer lives.

As a medical oncologist who is dedicated to the care of patients with advanced kidney cancer and bettering outcomes through clinical research, I am frequently asked 'What are the unmet needs for the treatment of advanced kidney cancer?'

FIVE UNMET NEEDS

First, complete remissions and long-lasting responses. Less than one-half of patients' tumours shrink after treatment, and it is usually a partial response in which some portion of the tumour remains. Complete remission — total disappearance of the tumour — is rare, and nearly all tumours progress within two years of starting treatment. In a phase III trial that compared two common first-line antiangiogenic drugs, pazopanib and sunitinib, the response rates were just 31% and 24%, respectively. For both drugs, fewer than 1% of patients experienced complete remission[3]. After two years, more than 75% of patients saw their tumours progress. New immunotherapies have been reported to achieve lengthy responses: in a phase III trial of nivolumab in people who had previously been given antiangiogenic therapy, the response rate was a modest 25%, but many of the responses were long-lasting[4]. Clinical trials of immunotherapy combinations and immunotherapy–antiangiogenic agents are under way, and may show improved durability of response and higher complete remission rates.

Second, biomarkers. No serum or tumour biomarker has been developed to guide treatment. Although the *VHL* gene is mutated or silenced in nearly all clear-cell renal cell carcinomas, and there are reports of other genes that may help to diagnose kidney cancer (for example, *BAP1*), none have been shown to predict the success of one targeted treatment over another. Identifying biomarkers could help doctors to choose the best drug for each clinical scenario, as well as to select new targets for therapy.

Third, a reduction in drug-related toxicity. Kidney cancer requires long-term care, and patients experience unpleasant side effects throughout their treatment. Fatigue, painful sores on the soles of the feet and diarrhoea are all associated with taking anti-angiogenic drugs and are particularly problematic for patients. Side effects differ depending on the drug, and in some cases can be avoided by drug choice. Pazopanib, for example, is associated with less fatigue and skin toxicity than sunitinib, but more liver toxicity[3]. In addition to producing drugs with a better safety profile, we need to better ascertain the mechanism of toxicity and how best to manage it. Immunotherapy drugs might show the way forward. Patients reported fewer moderately severe side effects with nivolumab, compared with the mTOR inhibitor everolimus[4]. This is an important finding because everolimus is regarded as one of the best-tolerated drugs for kidney cancer.

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Fourth, non-clear-cell renal cell carcinoma. Drug development has mostly been directed at the clear-cell type, which comprises 70–90% of renal cell carcinoma cases. The remaining cell types, collectively referred to as non-clear, include papillary, chromophobe and translocation subtypes. These tumours are uncommon, and the non-clear cell group as a whole is heterogeneous. There have, therefore, been few studies to define the underlying biology and clinical trials of new agents. This warrants more attention.

Fifth, early detection. There is no way of screening for kidney cancer to detect primary tumours or metastases early. Kidney cancer is commonly diagnosed during an ultrasound for an unrelated symptom. Nearly 20% of patients have distant metastases at the initial diagnosis, and an additional 20–30% of people will develop metastatic disease after surgery. A lack of screening to detect cancers early leads to a high proportion of patients who develop metastases, which usually turn out to be fatal.

As well as these five unmet needs, the cost of therapy needs to be lowered, we need a better understanding of the aetiology of kidney cancer, and we need to find a strategy for prevention. An increased awareness of these needs should foster greater efforts in clinical trials and basic research. ■

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