

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Emerging Targets in Kidney Cancer: Opportunities for Drug Development



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H&O How common is kidney cancer?

WS Kidney cancer, also known as renal cancer, is an unusual—although perhaps not rare—cancer. There are approximately 76,000 new cases in the United States every year, with approximately 14,000 deaths. Kidney cancer is one of many solid tumors that lack an established screening protocol. Patients with kidney cancer therefore present for diagnosis after a test such as computed tomography shows an incidental finding or they develop symptoms associated with more advanced or metastatic disease.

H&O What are the challenges in developing treatments for kidney cancer?

WS Many of the challenges are the same as for solid tumors in general. For many years, there was an incomplete understanding of the pathogenesis. Currently, we have a better understanding of the fundamental oncogenic pathways, which include inactivation of the von Hippel-Lindau (*VHL*) gene, mutations in the chromatin-modifying genes polybromo-1 (*PBMRI*) and BRCA1-associated protein 1 (*BAP1*), and alterations in the tumor immune micro-environment. However, we lack good drugs for directly targeting many of these abnormalities.

H&O What are the current targets and treatments in kidney cancer?

WS The major targeted agents are the vascular endothelial growth factor receptor (VEGFR) inhibitors, the programmed death 1 (PD-1) inhibitors, and the cytotoxic

T-lymphocyte-associated protein 4 (CTLA-4) inhibitors. The VEGFR inhibitors are probably better classified as multikinase inhibitors that target the VEGFR, the platelet-derived growth factor receptor, and other kinases. The PD-1 and CTLA-4 inhibitors have been especially impactful and have resurrected the long-term interest in immunotherapy for renal cancer.

For patients with advanced disease who require systemic therapy, the standard up-front treatments consist of a VEGFR inhibitor plus a PD-1 inhibitor or the PD-1 inhibitor nivolumab (Opdivo, Bristol Myers Squibb) plus the CTLA-4 inhibitor ipilimumab (Yervoy, Bristol Myers Squibb). Occasionally, patients are treated with monotherapy, most typically a VEGFR inhibitor. Patients who are refractory to initial therapy sometimes receive additional drugs from the same class because there is not complete cross-resistance. Treatment options also include the mammalian target of rapamycin inhibitor everolimus, but this drug is not very effective in this setting.

H&O Is there any research into new targets in kidney cancer?

WS There is ongoing work in this field. Hypoxia-inducible factor (HIF) is quickly emerging as a relevant therapeutic target. HIF upregulation is one of the most immediate downstream effects of the *VHL* mutation, which is the pathogenic lesion for renal cancer oncogenesis. In the kidney cancer setting, the HIF-2 α inhibitor belzutifan (Welireg, Merck) is approved by the US Food and Drug Administration for adults with *VHL* disease who require treatment for renal cell carcinoma. Ongoing

studies are evaluating whether treatment with this drug can be expanded to the more prevalent clear cell renal cancer. Researchers are also evaluating additional immune checkpoint inhibitors, such as the T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) and the lymphocyte-associated gene 3 (LAG3). Finally, there are emerging early data for bispecific antibodies.

H&O How might these novel agents address unmet needs in kidney cancer?

WS After a patient has been treated with a PD-1 inhibitor and a VEGFR inhibitor, there are few good standard therapies. The existing treatments are not curative. Palliative treatments can extend life. In some patients, immunotherapies appear to confer long-term survival. We are hoping that the long-term survival will be durable, but it is too early to tell. The vast majority of patients will develop progressive disease, and there are not many other treatments available.

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H&O Are there any other promising areas of treatment in kidney cancer?

WS The technology for administering focal radiation, also known as stereotactic body radiotherapy, has improved dramatically. This technology allows for the treatment of oligometastases. This term refers to 2 scenarios: a small number of metastases that are the only ones present or a lesion that is growing in a milieu of other metastatic sites that are responding to therapy.

H&O Are there other opportunities to improve treatment for patients with kidney cancer?

WS Many patients with kidney cancer receive palliative treatments for many years. It is important to discuss management of toxicities and survivorship issues. There has been a focus on ways to address the toxicities of these agents. Another important aspect is the cost of care. These medications are extremely expensive. How do we manage

costs, not only from a systems or insurance perspective, but also from an out-of-pocket perspective? A 10% copay for a \$40-a-month prescription is one thing. A 10% copay for a \$10,000-a-month medication that may be given for 12, 24, or 36 months is a much bigger issue. It is becoming increasingly important to address these kinds of questions.

The biggest unmet need is to develop novel screening approaches. These cancers tend to be diagnosed late because the patients are asymptomatic in early stages. Newer approaches, such as analysis of circulating DNA markers within the urine, are promising areas of research. The sensitivity and specificity of a screening test for a disease that is relatively unusual must be very stringent.

I am a member emeritus of the Kidney Cancer Association's Medical Steering Committee, and I am a strong supporter of this organization. The Kidney Cancer Association very effectively disseminates information, supports patients and their caregivers, and brings together the community of multidisciplinary physicians to address the needs in this disease.

Disclosure

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Suggested Readings

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