CURRENT AND EMERGING TREATMENT OPTIONS IN ADVANCED RENAL CELL CANCER*

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ABSTRACT

Because renal cell carcinoma (RCC) is highly resistant to chemotherapy, disease prognosis and patient life expectancy are poor. The general emphasis of therapy development has shifted from toxic cytokine therapies to novel molecular-targeted therapies. This review article discusses current and emerging targeted agents, including combination and sequential therapies, which show promise in the struggle against RCC. (Adv Stud Med. 2008;8(1):5-7)

In 2007, an estimated 40,000 people in the United States will be diagnosed with renal cell carcinoma (RCC), and close to 13,000 deaths will occur as a result of this disease.1 Despite its relatively low incidence, RCC is clinically significant because of the poor outcomes in patients with advanced disease. Once metastatic disease develops, cure for RCC is rare, and the median survival is approximately 1 year.1 However, considerable progress in the management of RCC has been achieved with new and emerging therapeutic strategies. Less invasive procedures are being used for the treatment of local disease and molecular-targeted therapies are being used for metastatic disease.2

ROLE OF VON HIPPEL-LINDAU GENE

Renal cell carcinoma is composed of several cancer types, with different histologies, clinical courses, response to therapy, and phenotypic characteristics.1 The most common type is clear cell renal carcinoma, which occurs in roughly 80% of patients and is associated with von Hippel-Lindau (VHL) gene mutation. The VHL gene protein (pVHL) regulates the transcription of hypoxia-inducible factor (HIF), or more specifically, the HIF-α and HIF-β subunits.4 Under hypoxic conditions or VHL mutations, HIF heterodimers accumulate and transcriptionally activate factors involved with hypoxia adaptations, such as vascular endothelial growth factor (VEGF) and other angiogenic factors. Nonmutated pVHL binds to cellular proteins (Figure 1), such as protein kinase C family members, collagen I and IV, and fibronectin, as well as with tailless complex polypeptide 1 ring complex. Additionally, pVHL complexes, such as those formed with protein NEDD8, regulate the cytoskeleton and extracellular matrix. Alterations in normal pVHL function may be linked to malignancies and represent an important target for therapeutic strategies.

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CURRENT TREATMENT APPROACH

Surgery continues to be the standard of care for localized RCC. Although cytoreductive nephrectomy followed by systemic therapy has become the standard of care for metastatic disease, this strategy may be changing yet again with regard to the timing of nephrectomy in patients on targeted agents.5 Currently, 4 agents are US Food and Drug Administration (FDA) approved for the treatment of RCC, including high-dose interleukin-2 (IL-2), sorafenib, sunitinib, and temsirolimus. Interferon α (IFNα) has been extensively used, and the monoclonal antibody bevacizumab is being investigated in the treatment of RCC; however, these agents are not currently US FDA approved for this indication.

HIGH-DOSE IL-2 AND IFNα

Until recently, high-dose IL-2 and IFNα, which are both cytokines, were the only agents that showed clinical benefit in patients with RCC.6 Although high-dose IL-2 is associated with a 4% durable complete response rate in selected patients, this agent is linked to severe toxicities that demand careful inpatient administration and monitoring.7 IFNα is associated with only a modest survival benefit despite significant toxicities, limiting its future use in RCC.

SORAFENIB

Sorafenib, the first US FDA-approved receptor tyrosine kinase inhibitor (RTKI) for the treatment of advanced RCC, demonstrated improved progression-free survival (PFS), compared to placebo (5.5 months and 2.8 months, respectively) in patients with metastatic RCC in whom previous treatment had failed.8 Based on the first PFS analysis, crossover to the treatment group was offered to patients in the placebo group at 18 months into the trial. Whereas overall survival was numerically higher in the treatment arm at the first and second interim analysis (before and after crossover was permitted), by intent-to-treat analysis the curves did not meet the threshold for significance at either interim analysis. Regardless, this trial demonstrated the benefit of RTKIs as second-line agents in...
improving PFS of patients with advanced clear-cell RCC.

A small phase II trial investigated sorafenib versus IFNα as first-line therapy for patients with advanced clear-cell RCC. The study design included the option of sorafenib dose escalation or crossover from IFNα to sorafenib. Median PFS for sorafenib versus IFNα was 5.7 months and 5.6 months, respectively. The PFS was not statistically significantly different between the groups (including the crossover and dose escalation groups), and this study failed to demonstrate the superiority of sorafenib over IFNα as first-line treatment for RCC.

**SUNITINIB**

A recent, phase III study evaluated the PFS of the RTKI sunitinib as compared to IFNα. The study population consisted of patients with metastatic clear-cell RCC with good-to-intermediate survival risk factors and without a history of systemic treatment for RCC. The PFS was 11 months for the sunitinib group versus 5 months for the IFNα group. Mature overall survival data are not yet available. Based on this trial, sunitinib, used as first-line therapy, appears to offer a PFS advantage in comparison to not only IFNα, but also to sorafenib.

**BEVACIZUMAB**

The AVOREN trial, a phase III study, evaluated bevacizumab in combination with IFNα as first-line treatment of metastatic RCC. Bevacizumab plus IFNα significantly increased PFS (10.2 months vs 5.4 months) and objective tumor response (30.6% vs 12.4%), as compared to placebo plus IFNα therapy. Although the incidence of treatment discontinuation as a result of adverse events was higher with bevacizumab plus IFNα compared to placebo plus IFNα (28% vs 12%, respectively), no unexpected safety events were observed. A trend toward improved survival was seen on the initial survival analysis favoring the study arm.

**TEMSIROLIMUS**

A phase III trial randomized previously untreated, poor-prognosis patients with
metastatic RCC to receive the mammalian target of rapamycin inhibitor temsirolimus, IFNα, or temsirolimus plus IFNα. Overall survival improved in the temsirolimus group as compared to the IFNα group (10.9 months vs 7.3 months, respectively), but no survival benefit was observed in the combination therapy group (8.4 months) as compared to IFNα.

Based on evaluation of new scientific data, the National Comprehensive Cancer Network (NCCN) expert panel continuously updates guidelines in oncology. NCCN guidelines for the treatment of kidney cancer are summarized in Figure 2. IFNα is currently no longer recommended as first-line therapy for RCC, except when used in combination with select agents.

**EMERGING THERAPIES**

Several therapies in various stages of clinical development show promise for the treatment of RCC.

**AXITINIB**

Axitinib, a potent RTKI of VEGF, was investigated in a phase II trial of patients with metastatic RCC refractory to sunitinib, including a subset of patients who also received prior sunitinib treatment. Partial response was observed in 14% of patients, with an overall 57% of patients experiencing some degree of tumor regression. Although a complete response has not yet been observed, this study does indicate that patients who fail to respond to one RTKI may respond to a different RTKI.

**PAZOPANIB**

Pazopanib, another potent RTKI with antitumor and antiangiogenic properties, was investigated in an ongoing phase II trial of patients with local or metastatic RCC who had no prior systemic treatment or who failed cytokine- or bevacizumab-based therapy. Patients randomized to placebo were allowed to cross over to pazopanib after a 12-week interim analysis, which indicated a 27% partial tumor response rate to pazopanib (by independent review) with an acceptable toxicity profile. The total disease control rate at 12 weeks (partial tumor response plus stable disease) was 73%.

**COMBINATION THERAPIES**

Combining newer targeted agents that show clinical benefit may be a useful therapeutic strategy against RCC. Several trials are investigating potential therapeutic combinations used either concomitantly or sequentially.

**BEST TRIAL**

This randomized phase II trial is comparing PFS of patients with advanced RCC treated with combinations of bevacizumab with temsirolimus and sorafenib versus bevacizumab alone. Perhaps the greatest challenge to date with this trial was determining maximally tolerated doses of the individual agents in the phase I setting. These doses were subsequently incorporated into an efficient algorithm of combination therapy for phase II investigation, results of which are greatly anticipated.

**SPARQ TRIAL**

This 6-arm study is examining the most effective sequence of agents (temsirolimus, sunitinib, or bevacizumab) in patients with metastatic RCC without prior therapy (Unpublished data, MD Anderson Cancer Center, 2007). Patients will receive temsirolimus, sunitinib, or bevacizumab up front, and at time of progression (TTP) 1, will be rerandomized to 1 of the 2 remaining agents, to determine TTP2. Although this study is not formally powered to study the magnitude of difference between the sequences, it uses innovative statistics to provide a highly accurate determination of which sequence provides the longest cumulative TTP.

**FUTURE RESEARCH DIRECTIONS**

To move the study of RCC forward requires the integration of tissue-rich, informative clinical trials with a more sophisticated means of evaluating tumor cell molecular biology and then applying this molecular understanding to the design of future clinical trials. For example, clinical trials that analyze the effects of targeted therapy on tumor tissue may permit us to predict which patients will show tumor response and resistance in forthcoming trials. These tissue-rich trials may not only permit enrichment of clinical data, but they also may save time and resources. Particular molecular pathways can therefore be targeted to improve tumor response and prevent therapy resistance.

**CONCLUSIONS**

Novel targeted therapies for metastatic RCC are clearly prolonging PFS and possibly overall survival. However, because there is still no definitive cure for RCC, clinical trials should continue to investigate drug combinations and sequences that improve patient outcomes. Robust, reliable, and informative biomarker discovery platforms are vital to the success of these trials.

**REFERENCES**


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