Novel Agents and Approaches for Advanced Renal Cell Carcinoma

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Purpose: Targeted agents have changed the treatment paradigm for advanced renal cell carcinoma. Approved agents with demonstrated efficacy are sunitinib, sorafenib, pazopanib, bevacizumab, temsirolimus and everolimus. However, there is an unmet need for new agents to improve the clinical outcome in treatment naïve patients and in those who are disease refractory or intolerant to traditional and targeted therapies. Many novel targeted agents, of which some have different mechanisms of action than approved agents, and immunomodulatory agents are currently in development for renal cell carcinoma.

Materials and Methods: We searched ClinicalTrials.gov to identify novel agents for advanced renal cell carcinoma in ongoing phase II/III clinical trials. Using the relevant agents as search terms we reviewed the medical literature for mechanisms of action and efficacy, and safety results to date, including data from recent major oncology meetings.

Results: A total of 11 novel targeted agents, including next generation tyrosine kinase inhibitors, and inhibitors of vascular endothelial growth factor ligand binding, Akt and endothelial cell proliferation, and 3 novel immunomodulatory agents, are under evaluation for renal cell carcinoma. In addition to ongoing phase II/III trials of emerging agents, head-to-head, crossover and combination trials of approved targeted agents are under way.

Conclusions: Although many agents are approved or in development for renal cell carcinoma, comparative effectiveness data are lacking. Ongoing and future head-to-head trials using appropriate comparators are essential to update renal cell carcinoma treatment guidelines. Future research should be aimed at identifying agents that improve patient outcomes and have decreased toxicity compared with currently approved agents with the goal of complete remission.

Key Words: kidney; carcinoma, renal cell; immunomodulation; antineoplastic agents; clinical trials as topic

Abbreviations and Acronyms

AE = adverse event
BID = twice daily
CR = complete response
FGFR = fibroblast growth factor receptor
IFN = interferon
mRCC = metastatic renal cell carcinoma
mTOR = mammalian target of rapamycin
ORR = objective response rate
PD-1 = programmed death-1
PDGFR = platelet-derived growth factor receptor
PFS = progression-free survival
PR = partial response
QD = once daily
RCC = renal cell carcinoma
SD = stable disease
TKI = tyrosine kinase inhibitor
VEGF = vascular endothelial growth factor
VEGFR = VEGF receptor

RENAL cell carcinoma accounts for 2% to 3% of cancers worldwide and the rate has increased 2% per year for the last 6 decades.[1] About 25% to 30% of patients with RCC present with mRCC at diagnosis.[2] Although the 5-year survival rate is 96% for patients with stage I RCC, it is only 23% for those with advanced disease.[1] Since advanced RCC is highly resistant to radiation and chemotherapy, historically the standard of care has been cytokine therapy. However, this treatment provides limited clinical benefit and is associated with significant toxicity.[1]

Elucidation of signal transduction pathways involved in RCC, including those leading to angiogenesis, the response to hypoxia, and cell proliferation and survival, has led to the de-

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velopment of targeted agents. Six agents have been approved to treat advanced RCC since 2005. Sorafenib, sunitinib, pazopanib and bevacizumab target the VEGF pathway, and temsirolimus and everolimus inhibit the mTOR pathway.

Despite the promise of approved targeted therapies a complete response is rare and patients often become resistant/refractory to first line treatment.[3] New agents with improved efficacy and decreased toxicity are needed as treatment options in first line or subsequent settings. Multiple targeted and immunomodulatory agents are in phase II/III development for advanced RCC. An update on emerging agents and ongoing clinical trials of new and approved therapies is provided.

METHODS

Identifying Clinical Trials for Advanced RCC

We searched the ClinicalTrials.gov registry on May 31, 2011 using the terms renal cell carcinoma, renal cell cancer or RCC. The search was refined by recruitment (open studies), study type (interventional), condition (renal cell carcinoma or RCC) and trial phase (phase II or III). These criteria yielded 553 trials, which were evaluated manually. Trials were included in analysis if they evaluated patients with advanced RCC and with clear cell histology, which accounts for 80% to 90% of those with RCC,[4] and if the study drug was an agent with a molecular target thought to be involved in disease pathogenesis (targeted agent) or an immunomodulatory agent.

Literature Searches

The PubMed® database was searched for each agent of interest and RCC, renal cell carcinoma or renal cell cancer. It was restricted to English language publications. The Science Citation Index Expanded™ database (2001 to present) and the Conference Proceedings Citation Index^{SM}-Science database (2006 to present), which archive abstracts presented at select oncology and urology meetings, and the American Society for Clinical Oncology Annual Meeting abstract database were also searched for relevant agents.

RESULTS

Emerging Agents

We identified 11 novel targeted agents in phase II/III development, including next generation TKIs that target VEGFR, FGFR and PDGFR as well as inhibitors of VEGF ligand binding, Akt and endothelial cell proliferation (fig. 1, *A*). Alterations in multiple signaling pathways may contribute to RCC and differ among patients with RCC. Agents that target pathways other than the VEGF or mTOR pathway may be more effective in particular patient subsets depending on the tumor profile. They may be a useful strategy in those resistant to first line agents. We identified 3 novel immunomodulatory agents that augment antitumor immune responses or block checkpoints that inhibit immune responses (fig. 1, *B*).

Targeted Agents in Phase III Development

Axitinib (AG-013736). Axitinib is a potent, selective, second generation inhibitor of VEGFR-1, 2 and 3.[5] In phase II studies of axitinib as second line treatment for sorafenib[6] and cytokine[7] refractory RCC, the ORR was 22.6% and 44.2%, respectively. In 62 patients with sorafenib refractory RCC median PFS was 7.4 months (95% CI 6.7, 11.0). Common nonhematological AEs were fatigue in 77.4% of cases, diarrhea in 61.3%, anorexia in 48.4%, hypertension in 45.2% and nausea in 43.5%.[6] Most AEs were grade 2 or less.

In 52 patients with cytokine refractory RCC median time to progression was 15.7 months (95% CI 8.4, 23.4).[7] Common treatment related AEs were diarrhea in 59.6% of cases, hypertension in 57.7%, fatigue in 51.9% and nausea in 44.2%. At the conclusion of the study 24 patients were alive, including 11 who received long-term axitinib therapy in a continuing access protocol. At a median followup of 5.9 years updated survival data indicated a 5-year survival rate of 20.6% (95% CI 10.9, 32.4).[8]

An ongoing phase II study (NCT00569946) is investigating axitinib in Japanese patients with cytokine refractory RCC.[9] Interim analysis showed an ORR of 55%. Commonly reported AEs were hand-foot syndrome in 73% of cases, hypertension in 66%, diarrhea in 66% and hoarseness in 53%.

In the international phase III AXIS (Axitinib [AG 013736]as Second Line Therapy for Metastatic Renal Cell Cancer) study 723 patients with RCC refractory to a sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokine based regimen were randomized to axitinib (361) or sorafenib (362) as second line therapy.[10] Patients who received axitinib had significantly longer PFS (6.7 vs 4.7 months, HR 0.665, $p < 0.0001$). Safety and quality of life profiles were comparable.[10,11] The international phase III AGILE (Axitinib [AG 013736]for the Treatment of Metastatic Renal Cell Cancer) trial (NCT00920816) is comparing axitinib with sorafenib for first or second line mRCC. Results are expected in 2012.

Current research is aimed at optimizing axitinib exposure in patients with RCC. In an ongoing phase II trial (NCT00835978) about 200 treatment naïve patients with RCC will receive a standard starting dose of axitinib (5 mg BID) in an initial 4-week cycle.[12] Those with blood pressure 150/90 mm Hg or less, no grade 3/4 treatment related toxicity, no dose reductions during the initial 4-week cycle and 2 or less concurrent antihypertensive medications will be randomized to dose up titration with axitinib or placebo using a prespecified scheme.