Kidney Cancer Targeted with New VEGF Inhibitor

Early stage trials had shown that cediranib (Regorafenib), a new VEGF tyrosine-kinase inhibitor, may be helpful in treating patients with refractory breast cancer, colorectal cancer, glioblastoma, acute myeloid leukemia, and non–small cell lung cancer (NSCLC). Now, a phase II study by researchers from the United Kingdom and The Netherlands has examined the efficacy of cediranib in patients with advanced renal cell cancer (RCC).

In this double-blind, parallel-group study, 53 patients with metastatic or recurrent renal cell carcinoma were randomized to receive monotherapy with 45 mg of cediranib per day, and 18 patients were given a placebo for the course of the study. After 12 weeks of treatment, the researchers noted a significant change in tumor size from baseline in patients taking cediranib compared with those on placebo. The patients in the cediranib group demonstrated a mean 20.4% decrease in tumor bulk, and the patient with the greatest tumor shrinkage saw a 31% in tumor size by the end of the trial. Conversely, patients taking placebo experienced a mean 19% increase in tumor size ($P < .0001$). Patients in the placebo group were given the option of crossing over to cediranib after 12 weeks or signs of progression. According to the researchers, “Ten of the fourteen individuals who opted for the cediranib treatment had a substantial decrease in the tumor size.”

They reported that 18 patients (34%) in the cediranib arm had a partial response, but no one had a complete response. In addition, 25 (47%) of patients achieved stable disease. Patients receiving treatment with cediranib also exhibited significantly greater median progression-free survival (PFS) compared with patients in the placebo group, at 12.1 months versus 2.7 months, respectively (HR, 0.45; $P = .017$). On the basis of results from this phase II study, the researchers concluded that oral cediranib monotherapy is an effective treatment for advanced RCC.

There were safety concerns, however, with investigators reporting that 82% of patients in the cediranib cohort required dosage reductions or treatment interruptions because of adverse effects. More than half (57%) experienced grade 3 or higher grade adverse events, of which fatigue, hypertension, and diarrhea were most common. Three patients developed reversible posterior leukoencephalopathy syndrome, associated with some existing antiangiogenesis agents. Although the starting dose was 45 mg of cediranib daily, after reductions, the mean dose was 35 mg daily. Only 20 patients remained on 45 mg per day at interim analysis.

One of the discussants for the session, David Nanus, MD, Weill-Cornell Medical College, New York, expressed concern about the drug’s toxicity. He suggested other VEGF inhibitors might have a better safety profile. Another discussant, Philip Walther, MD, PhD, Duke University, Durham, North Carolina, disagreed, however. “The safety-tolerability profile is very predictable,” he said, referring to other trials investigating cediranib. A planned phase III trial in NSCLC was scrapped by the manufacturer because of concerns about toxicity.

Regorafenib Shows Strong First-line Activity in Metastatic RCC

In a phase II study of metastatic renal cell carcinoma (RCC), the oral multikinase inhibitor regorafenib (BAY 73-4506) produced disease regression or stabilization in 81% of patients. Results were reported by Tim Eisen, PhD, of Addenbrooke’s Hospital at the University of Cambridge, United Kingdom.

“This study suggests regorafenib has encouraging activity as a potential first-line treatment option for advanced RCC. I am excited about the potential of this compound,” Dr Eisen said.

The drug is an oral multi-kinase inhibitor that targets angiogenic, stromal, and oncogenic receptors. The distinct anti-angiogenic profile includes inhibition of both VEGF receptor 2 and TIE2 tyrosine kinase. “TIE2 is redundant with VEGF,” he explained, “and is an escape mechanism for the tumor that may well be worth inhibiting” in several tumor types.

The study included 49 patients with previously untreated, unresectable or metastatic RCC, predominantly clear cell histology. Treatment consisted of 160 mg of regorafenib once daily for 3 weeks, followed by 1 week off, until progression. At screening, 23 patients had a “low risk” and 26 an “intermediate risk” Memorial Sloan Kettering Cancer Center score.

In this final efficacy analysis, median progression-free survival (PFS) was 8.3 months. A confirmed partial response (PR) was observed in 15 (31%) patients; 2 additional patients had a PR after the formal study cut-off, increasing the PR rate to 35%. Half the patients had stable disease, yielding a disease control rate of 81%. Only 5 (10%) patients progressed and 4 (8%) were not assessable, Dr Eisen reported.

Many confirmed responders maintained response for 5 to 9 months, “giving a hint that benefit is often prolonged in those who do respond,” he noted, adding that 80% of patients with a PR continued to maintain their response at final analysis. Some patients experienced stable disease for >5 months, and a degree of tumor shrinkage was observed in 89% of patients.

Adverse events were typical of this drug class and considered manageable. Hand-foot skin reactions were observed in 65% of patients (grade 3 in 29%), which Dr Eisen said was “more easily managed” than in patients receiving other tyrosine kinase inhibitors (TKIs). Fatigue, however, was reported by 51%, and Dr Eisen said this effect may be somewhat worse with regorafenib than with other TKIs.

Other common adverse effects were hypertension, mucositis, diarrhea, and alopecia. Renal failure occurred unexpectedly in 4 patients, which investigators attributed to dehydration from a rotovirus infection at one study site.


Multikinase Inhibitor Pazopanib Effective in Kidney Cancer

Researchers conducting a phase III trial of the multikinase inhibitor pazopanib (Votrient) found that the drug improved outcomes in patients with clear cell advanced renal cell carcinoma. A previously reported phase II trial by Hutson et al showed that nearly three-quarters of patients treated with pazopanib for 12 weeks achieved partial response or stable disease, and this provided the rationale for additional studies.

The phase III trial included 233 treatment-naïve patients and 202 patients who had previously received cytokine therapy. Patients were randomized to receive 800 mg daily of pazopanib (n = 290) or placebo (n = 145). The investigators found that overall progression-free survival (PFS) for patients receiving pazopanib was nearly 5 months longer than for patients in the placebo group (Table 1). Results were then stratified according to whether patients had received prior treatment. Data indicated that the PFS advantage was greater for untreated patients who received pazopanib than for previously treated patients when compared with their counterparts taking placebo. These results were reported earlier this year at the ASCO Annual Meeting in May 2009 by lead author Cora N. Sternberg, MD, chief of the Department of Medical Oncology, San Camillo and Forlanini Hospitals in Rome, Italy. Describing survival outcomes at the meeting, Dr Sternberg said, “The study shows that pazopanib significantly improved PFS for patients regardless of whether or not they had prior therapy. While there have been many treatment advances for patients with advanced kidney cancer, there is still a need for medicines that are effective and well tolerated.”

For the most recent analysis, investigators attempted to determine what factors, if any, might predict favorable response to pazopanib. They assessed response rates (RRs) for subgroups based on hemoglobin level, age, sex, Memorial Sloan Kettering Cancer Center (MSKCC) risk group, European Cooperative Oncology Group performance status (ECOG PS), number of disease sites, and the interval between initial diagnosis and starting therapy (Table 2).

They found that patients taking pazopanib who had favorable MSKCC risk scores had a better RR than those with intermediate risk scores (42.5% vs 33.3%, respectively; P = .1) and improved PFS (14.8 mo vs 5.6 mo, respectively; P = .0002). Additionally, ECOG PS 0 was associated with a higher response rate than ECOG PS 1 (43.9% vs 29.3%, respectively; P = .013) and improved PFS (14.8 mo vs 7.4 mo, respectively; P = .0287). A hemoglobin level at or above the lower limit of normal also correlated with improved response compared with a level below the lower limit of normal (41.0% vs 29.1%; P = .037), and superior PFS (12.9 mo vs 7.4 mo, P = .0289). Patients who waited more than a year from diagnosis to treatment had better outcomes than those treated within the first year, with a response rate of 40.0% versus 28.8%, respectively (P = .068) and a median PFS of 12.9 months versus 7.4 months, respectively (P = .0289). The number of disease sites was the only factor investigated that did not correspond to improved outcomes with pazopanib.

Pazopanib was approved by the FDA in October 2009 for patients with advanced kidney cancer. Common adverse reactions include diarrhea, high blood pressure, hair color changes, nausea, loss of appetite, vomiting, fatigue, weakness, abdominal pain, and headache. It may also contribute to liver toxicity.


Using Algorithms to Diagnose Bladder Cancer

Single biomarkers have some value in diagnosing bladder cancer, but researchers from Ireland decided to look for a better and more accurate way. They used computerized algorithms to check for a constellation of markers, signs, and symptoms. Initial research has shown that multivariate algorithmic classification for bladder cancer has high diagnostic accuracy.

The researchers conducted a case-controlled study of 161 patients, ranging in age from 19 to 84 years, underwent cystoscopy to evaluate hematuria. Nearly half the patients (48%) had negative cystoscopy, negative pathology, or both. Pathologic examination showed bladder cancer in 52%, with 53 patients staged at pT1G2 and 31 staged at pT1G3.

Blood and urine samples were obtained from each study participant and multiple analyses were performed, including nuclear matrix protein 22 (NMP22), cytology, protein creatinine levels, osmolality, carcinoembryonic antigen (CEA), free PSA, and total PSA. The investigators noted several differences between control and case subjects. Whereas levels for most laboratory tests were higher in the patients with bladder cancer, the levels of C-reactive protein and endothelial growth factor (EGF) were significantly higher in controls (P < .05). The researchers also found that longer and heavier smoking history and the use of antihypertensive medication was associated with a greater likelihood of a bladder cancer diagnosis.

The highest sensitivity of any individual biomarker or test was 68%, and the highest specificity was 95%. NMP22 levels were the best-rated biomarker in terms of sensitivity, but cytology had the highest specificity. Using logistic regression analysis, the researchers incorporated 9 biomarkers into the algorithm, including CEA, D-dimer, EGF, interleukin-2, monocyte chemoattractant protein-1, neuron-specific enolase, NMP22, thrombomodulin, vascular EGF, and von Willebrand factor. Added to this was the number of years a patient had smoked and whether the patient used antihypertensive medication.

The calculations revealed that these algorithms achieved sensitivities of 73% to 88% and specificities of 72% to 81%. The researchers established that multivariate algorithmic classifiers are effective in identifying patients who are likely positive for bladder cancer. They noted that this appears to be the first time an antihypertensive medication has been connected to a diagnosis of bladder cancer.

Genitourinary Cancers

Web Resources

National Kidney Foundation
www.kidney.org

The National Kidney Foundation Website explains the facts about chronic kidney disease (CKD), what causes it, its symptoms, how the kidneys help the body maintain health, and how one can lower the risk of developing kidney disease. A heading titled Professionals leads to subcategories such as Kidney Learning Solutions, Clinical Trials, Clinician Tools, Clinical Practice Guidelines, and relevant CME activities. The News and Events section presents the latest press releases as well as information on upcoming meetings and events.

Mayo Clinic: Bladder Cancer
http://tinyurl.com/2f6gm5

Ranging from basic to in-depth, the Mayo Clinic presents physicians with all the current information on bladder cancer. Topics on this include descriptions of the disease's symptoms, risk factors and causes, diagnoses and tests, complications, treatments and medications, and prevention. The Website also features patient-centered areas on coping and support. Physicians can also read about complementary and alternative approaches to bladder cancer prevention that are being researched.

Testicular Cancer
www.tc-cancer.com

Touted as “your testicular cancer resource network,” TC cancer.com provides a detailed description of the several different ways to treat testicular cancer, including orchiectomy, retroperitoneal lymph node dissection, and chemotherapy. The site explains how chemotherapy is administered and how it works. The site also features a selection of articles on the disease and a section containing the latest news in testicular cancer and treatments.

American Cancer Society: What is Wilms' Tumor?
http://tinyurl.com/ycm49pn

The American Cancer Society provides a detailed guide on Wilms' tumor, also called nephroblastoma, which is a type of cancer that starts in the kidneys and most commonly affects children. In addition to listing key statistics on the incidence of the disease, the site details its causes and risk factors and discusses prevention. The site also addresses the importance of early detection and provides information on diagnosis and staging; treatment options by type and stage of disease; and clinical trials.

UroToday
www.urotoday.com

UroToday's mission is to create a free, credible, referenced online publication that provides global open access to accurate and timely urological disease information. To that end, its Website provides information on many types of cancer, including prostate, bladder, renal, testicular, penile, and urethral. UroToday also features daily updated headlines in the world of urological cancers, an events calendar, and extensive conference coverage with detailed slide presentations and highlights.