Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles in this section were selected by the Guest Editor, Bernard Escudier, MD, for their timeliness, importance, and relevance to clinical practice or translational research.

Patient Outcomes Improved With Targeted Therapy

Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. *Drugs R D*. 2011; 11:113-126.

In the past few years, patient outcomes have significantly improved with the use of targeted agents for the treatment of advanced renal cell carcinoma (RCC). Several targeted agents are licensed for the treatment of metastatic RCC (mRCC), and a number of new agents are under investigation. Axitinib, a small molecule indazole derivative is an oral, potent multitargeted tyrosine kinase receptor inhibitor that selectively inhibits vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 at subnanomolar concentrations, in vitro. In various nonclinical models, axitinib has demonstrated in vivo target modulation and antiangiogenesis.

Pharmacokinetic studies have shown that 5 mg twice daily continuous daily dosing of axitinib administered orally with food, is rapidly absorbed and reaches peak concentrations within 2 to 6 hours.

Axitinib is metabolized primarily in the liver via the cytochrome P450 (CYP) system and less than 1% of the drug passes unchanged in the urine. The pharmacokinetics of axitinib do not appear to be altered by coadministered chemotherapies, and antacids do not have a clinically significant effect. Coadministration with CYP3A4 and 1A2 inducers is contraindicated. In addition, proton pump inhibitors reduce the rate of axitinib absorption.

Increased axitinib exposure is associated with higher efficacy indicated by decreased tumor perfusion and volume. In phase 2 clinical trials in patients with advanced RCC previously treated with cytokines, chemotherapy, or targeted agents, axitinib provided antitumor activity with a favorable noncumulative toxicity profile. In one study of patients with cytokine-refractory mRCC, an objective response rate (ORR) of 44.2% (95% CI 30.5, 58.7) was achieved. The median time to progression was 15.7 months (95% CI 8.4, 23.4) and the median overall survival (OS) was 29.9 months (95% CI 20.3, not estimable).

In another study of patients with sorafenib-refractory mRCC, ORR was 22.6% (95% CI 12.9, 35.0). The median progression-free survival (PFS) was 7.4 months (95% CI 6.7, 11.0 months) with a median OS of 13.6 months (95% CI 8.4, 18.8).

In a third study of patients with cytokine-refractory mRCC the ORR was 55% and median PFS was 12.9 months (95% CI 9.8, 15.6).

The most common adverse events in the 3 studies were fatigue, hypertension, hand-foot syndrome (HFS), and gastrointestinal toxicity. These were generally manageable with standard medical intervention. Of note, the incidence of HFS and proteinuria in the third study was higher than that reported in the second study in cytokine-refractory mRCC patients.

An observed association between diastolic blood pressure ≥ 90 mmHg and increased efficacy suggests potential use as a prognostic biomarker. However, this requires further investigation. Two randomized phase 3 clinical trials are ongoing to determine the efficacy of axitinib in patients with mRCC as first- and second-line treatment. These results will help to determine the place of axitinib in the mRCC treatment algorithm.

Targeted Therapy Results for Xp11 Translocation RCC

Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network. *Ann Oncol*. 2010;21:1834-1838.

Fifteen percent of patients younger than 45 years who have renal cell carcinoma (RCC) are affected with the Xp11 translocation subtype. The reserachers analyzed the benefit of targeted therapy (vascular endothelial growth factor receptor [VEGFR]-targeted agents and/or mammalian target of rapamycin [mTOR] inhibitors) in these patients.

Patients with Xp11 translocation/TFE3 fusion gene metastatic RCC who had received targeted therapy were identified. Nuclear TFE3 positivity was confirmed by reviewing pathology slides. Responses according to RECIST criteria, progression-free survival (PFS), and overall survival (OS) were analyzed.

Overall, 53 patients were identified; 23 had metastatic disease, and of these, 21 received targeted therapy (median age 34 years). Seven patients achieved an objective response. In first line, median PFS was 8.2 months (95% CI 2.6-14.7 months) for sunitinib (n = 11) versus 2 months (95% CI 0.8-3.3 months) for cytokines (n = 9; log-rank P = .003).

Further treatment (second, third, or fourth line) results were as follows: all 3 patients who received sunitinib had a partial response (median PFS 11 months). Seven of the 8 patients who received sorafenib had stable disease (median PFS 6 months). One patient who received mTOR inhibitors had a partial response, and 6 patients had stable disease. Median OS was 27 months with a 19 months median follow-up.

Study findings indicate that in Xp11 translocation RCC, targeted therapy achieved objective responses and prolonged PFS similar to those reported for clear-cell RCC.

New Cancer Genes Identified

Varela I, Tarpey P, Raine K, et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. *Nature*. 2011; 469: 539-542.

The genetics of renal cancer is dominated by the inactivation of the VHL tumor suppressor gene in clear cell carcinoma (ccRCC), the most common histological sub-

(continued on page 95)

(continued from page 83)

type. A recent large-scale screen of 3500 genes by PCR-based exon resequencing identified several new cancer genes in ccRCC including *UTX* (ie, *KDM6A*), *JARID1C* (ie, *KDM5C*), and *SETD2*. These genes encode enzymes that demethylate (*UTX*, *JARID1C*) or methylate (*SETD2*) key lysine residues of histone H3. Modification of the methylation state of these lysine residues of histone H3 regulates chromatin structure and is implicated in transcriptional control. However, these mutations are present in fewer than 15% of ccRCC, which suggests the existence of additional, currently unidentified cancer genes.

Varela and colleagues sequenced the protein coding exome in a series of primary ccRCC and identified the SWI/SNF chromatin remodelling complex gene *PBRM1* as a second major ccRCC cancer gene, with truncating mutations in 41% (92/227) of cases. These data further elucidate the somatic genetic architecture of ccRCC and emphasize the marked contribution of aberrant chromatin biology.

A Biomarker for Efficacy

Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst*. 2011;103:763-773.

Hypertension (HTN) is an on-target effect of the vascular endothelial growth factor pathway inhibitor, sunitinib. Rini and colleagues evaluated the association of sunitinib-induced HTN with antitumor efficacy and HTN-associated adverse effects in patients with metastatic renal cell carcinoma (mRCC).

The retrospective analysis included pooled efficacy (n = 544) and safety (n = 4917) data from 4 studies of patients with mRCC who were treated with 50-mg sunitinib daily, administered on a 4-week-on 2-week-off schedule. Blood pressure (BP) was measured in the clinic on days 1 and 28 of each 6-week cycle. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier analysis; hazard ratios (HRs) for survival were also estimated by Cox proportional hazards analysis using HTN as a time-dependent covariate. Efficacy outcomes were compared between patients with and without HTN (maximum systolic BP [SBP] ≥ 140 mmHg or diastolic BP [DBP] ≥ 90 mmHg). Adverse effects were also compared between patients with and without HTN (mean SBP ≥ 140 mmHg or mean DBP ≥ 90 mmHg). All *P* values were 2-sided.

Patients with mRCC and sunitinib-induced HTN defined by maximum SBP had better outcomes than those without treatment-induced HTN (objective response rate: 54.8% vs 8.7%; median PFS: 12.5 months, 95% CI = 10.9 to 13.7 vs 2.5 months, 95% CI = 2.3 to 3.8 months; and OS: 30.9 months, 95% CI = 27.9 to 33.7 vs 7.2 months, 95% CI = 5.6 to 10.7 months; $P < .001$ for all). Similar results were obtained when patients were compared with vs without sunitinib-induced HTN defined by maximum DBP. In a Cox proportional hazards model using HTN as a time-dependent covariate, PFS (HR of disease progression or death = .603, 95% CI = .451 to .805; $P < .001$) and OS (HR of death = .332, 95% CI = .252 to .436; $P < .001$) were improved in patients with treatment-induced HTN defined by maximum SBP; OS (HR of death = .585, 95% CI = .463 to .740; $P < .001$) was improved in patients with treatment-induced HTN defined by maximum DBP, but PFS was not.

Few any-cause cardiovascular, cerebrovascular, ocular, and renal adverse effects were observed. Rates of adverse effects were similar between patients with and without HTN defined by mean SBP; however, hypertensive patients had somewhat more renal adverse effects (5% vs 3%; $P = .013$).

In patients with mRCC, sunitinib-associated HTN was found to be associated with improved clinical outcomes without clinically significant increases in HTN-associated adverse events. These findings support its viability as an efficacy biomarker. KCJ