RENAL CELL CARCINOMA IN FOCUS

Section Editor: Robert A. Figlin, MD

Highlights from the Eigth International Kidney Cancer Symposium

Thomas Hutson, DO, PharmD, FACP
Director
Texas Oncology-Baylor Charles A. Sammons
Cancer Center
Dallas, Texas

TH We now have 6 new drugs that have been approved for the management of advanced kidney cancer in just about 4 years. These new therapies have improved the outcome for patients with this disease beyond what we had accomplished with traditional cytokine-based treatments (interferon and interleukin-2). From here, there are only a few ways that we can move forward: make more drugs that are more active, or find ways in which to use our current armamentarium of drugs better. Several new drugs are in development for renal cell carcinoma (RCC), including both vascular endothelial growth factor (VEGF)-directed therapies as well as therapies that work on other targets we believe to be important in the pathogenesis of this cancer.

At the Kidney Cancer Association's (KCA) Eighth International Kidney Cancer Symposium, which was held September 25-26, 2009, in Chicago, my colleagues and I presented follow-up data on some patients who had treatment-refractory disease, a subset where there are many unmet needs. Our data suggested that perifosine (KRX-0401, KERYX Biopharmaceuticals), an inhibitor of AKT, may be a drug with activity in a highly refractory patient population.

At the American Society of Clinical Oncology (ASCO) meeting earlier this year, my colleagues and I reported that perifosine treatment resulted in stable disease or better response in almost half of a group of RCC patients (n=16) who had progressed during treatment with a VEGF inhibitor and a mammalian target of rapamycin (mTOR) inhibitor. Patients received 100 mg of perifosine daily and were evaluated every 12 weeks. Patients who had objective response or stable disease continued treatment until the disease progressed or unacceptable toxicity developed.

We reported at the KCA meeting that perifosine led to 1 partial response and stable disease in half of the patients who had progressed after treatment with at least 2 prior therapies. Patients who achieved stable disease or a better response had a median progression-free survival (PFS) of 33 weeks. All but 2 patients remained alive as of late September, and the median overall survival (OS) had not been reached.

H&O What were the main highlights of the 2009 Kidney Cancer Association meeting?

TH What was most emphasized at the KCA meeting was the ongoing research of biomarkers and resistance. The ideas of molecular profiling and finding biomarkers are steps towards finding a way to predict which individual patients respond to certain therapies.

Currently, the best drug option for a patient is found by trial and error. We start the patient with one drug, and if it works, we continue it. At some point it may stop working, which is when we move on to the next drug. The hope for biomarkers is to individualize therapy for the patient. A biomarker may determine whether the drug is working or not; a biomarker in a tumor may be able to predict which drugs or which sequence of drugs will be ideal to treat the patient. These are reasons why research in the RCC field, as well as other types of cancer, is moving towards this concept of individualizing treatment based on molecular profiles.

Hypertension

In a retrospective analysis, investigators found a correlation between transient hypertension and improved survival in patients with metastatic RCC who were treated with sunitinib (Sutent, Pfizer), supporting the hypothesis that hypertension is a viable biomarker of antitumor efficacy in this patient population.

To investigate this association, Dr. Brian Rini and colleagues retrospectively analyzed pooled data for 544 patients with metastatic RCC treated with first-line or second-line sunitinib. Antitumor efficacy consisted of PFS, OS, and objective response rate. Hypertension was defined by the maximum and the mean blood pressure (systolic and diastolic). The efficacy analysis showed that patients with a maximum systolic pressure of 140 mm Hg or higher had a median OS of 30.5 months compared with 7.8 months in patients without systolic hypertension (P<.0001). With respect to diastolic pressure, a maximum

pressure of 90 mm Hg or higher was associated with a median OS of 32.1 months compared with 15 months in patients who did not have hypertension (P<.0001). Median PFS was 12.5 months and 13.4 months in patients with systolic and diastolic hypertension, respectively, versus 2.5 months and 5.3 months in patients without hypertension (P<.0001). Objective response rates were 54.7% and 57.2% with hypertension compared with 9.7% and 25% without hypertension (P<.0001).

Data revealed no clear risk of hypertension-associated complications in the sunitinib-treated patients, and the use of antihypertensive medication did not affect the antitumor efficacy of the targeted agent. The effect has not been associated with changes in cardiac structure or function.

VHL Wild Type, HIF1a/HIF2a, HIF2a

In her presentation at the KCA meeting, Dr. Kimryn Rathmell stressed that there is clinical heterogeneity even within the clear cell RCC subset, considering the variable risks for recurrence, metastatic disease activity, and response to therapy. Clear cell RCC is homogeneous in the fact that most of the clear cell histology tumors have a mutation in the VHL gene, leading to the upregulation of HIF factors (which are transcription factors that activate a wide repertoire of hypoxia target genes such as VEGF, platelet-derived growth factor [PDGF], and carbonic anhydrase IX [CAIX]). However, what is often overlooked is that VHL inactivation leads to the upregulation of an entire family of HIF factors, those best understood being HIF1a and HIF2a. HIF1a and HIF2a, while they have common targets like VEGF, PDGF, and CAIX, have specific targets of their own. In particular, HIF1a can upregulate the transcriptional activation of glycolysis enzymes such as hexokinase, phosphofructokinase, and LDH. HIF2a has its own unique targets, one notably being OCT4, a transcription factor involved in preserving a de-differentiated state.

Dr. Rathmell and her team found that there were 3 different classes of tumors of which they observed 1:1:1—VHL wild type, a VHL mutant where both HIF1a and HIF2a are expressed, and a VHL mutant where only HIF2a is expressed. They found that clear cell RCCs with intact VHL, as well as tumors with HIF1a/HIF2a signature, exhibited enhanced Akt/mTOR and ERK/MAPK signaling. Ki-67 staining was performed to quantify cell proliferation, and a 55% increase in Ki-67+ nuclei was observed in HIF2a tumors, relative to HIF1a/HIF2a tumors. The clearest difference was between low stage tumors, which displayed approximately 60% more Ki-67+ nuclei in HIF2a tumors than in VHL wild type or HIF1a/HIF2a tumors.

Those types that have any HIF signature—any VHL mutation—demonstrated upregulation in genes that involve angiogenesis, but those that have only a HIF2a signature particularly displayed a group of

genes responsible for enhanced cell cycle and DNA damage response. The HIF1a/HIF2a signatures were also unique with upregulation of genes that involved ribosome biosynthesis, protein translation, mTOR signaling, and glycolysis. Therefore, it was suggested that not all VHL mutations promote the same profile of HIF stabilization. HIF2a and HIF1a/HIF2a tumors elicit distinct patterns of cell signaling, and these distinctions may be important for predicting tumor behavior and designing individualized therapy.

Gene Clusters: ccA and ccB

Another biomarker that Dr. Rathmell and her team presented at the KCA meeting was discovered from gene expression profiling. Investigators searched for differences between tumors they could find on a molecular level. With a novel mechanism of pattern recognition using a machine-learning algorithm called ConsensusCluster, they looked at 2 highly distinct groups based on iterative pattern recognition (300 samplings for 52 samples): ccA and ccB. Analyzing these 2 distinct tumors, they found that compared to known biomarkers such as stage or performance status, this classification status bore out as a statistically significant variable in their multivariate analysis, correlating with survival. As a conclusion, they have now identified biomarkers called ccA and ccB, which are novel expression tools that define robust subdivisions of clear cell RCC. This classification score can be defined with a small number of genes on individual tumors and is independently associated with disease-specific and overall survival. Dr. Rathmell's presentation summarized how there are multiple ways to segregate clear cell RCC based on molecular phenotypes, and that defining these profiles for patients may aid in selecting a clinical strategy as treatment options become more complex.

Plasma/Serum-based Biomarkers

In his presentation at the KCA meeting, Dr. Mehrdad Khajavi introduced the advantages of blood-based biomarkers. The key advantages of studying blood-based or serum-based biomarkers are that they are noninvasive, samples are easy to collect and to store, clinicians can use commercially available assays to cross validate the results, and most importantly, they are applicable to large randomized trials.

To prove the concept of this hypothesis, Dr. Khajavi and colleagues collected blood samples in a trial that studied patients with metastatic clear cell RCC who had no prior systemic therapy. Patients were randomized 1:1 to sorafenib (Nexavar, Bayer; 400 mg twice a day) or sorafenib plus interferon. Samples were collected at baseline, 4 weeks, and 8 weeks. Patients were treated until disease progression or unacceptable toxicity. An exploratory analysis of 52 plasma cytokines and angiogenic factors (CAF) was conducted in order to derive a set of markers that would aid in determining whether patients should be treated with a combination

or a single agent. Investigators used a multiplexed bead suspension array, which has characteristics similar to flow cytometry and suspension ELISA; PFS was the outcome measured in this correlation analysis.

Study findings showed that at baseline, the concentration of the markers had some correlation with PFS. The researchers observed that in the single-agent arm, VEGF was increased with sorafenib treatment and soluble vascular endothelial cell growth factor receptor 2 (VEGFR2) was decreased. However, when the combination arm was analyzed, for soluble VEGF2, the effect of sorafenib was blunted with the addition of interferon. The researchers also found that combination treatment increased CAIX. Two predictive markers—osteopontin (OPN) and VEGF—were identified when the median concentration was used as a cut off. In patients receiving sorafenib plus interferon, those with OPN below the median concentration had better PFS than those who had high OPN; however, in patients who only received sorafenib, OPN concentration did not provide additional information.

The study also identified a set of 6 markers—OPN, VEGF, soluble CAIX, collagen 4, TRAIL, and soluble VEGFR2. In order to create a biomarker expression index, each marker was labeled as either positive (high concentration, 1) or negative (low concentration, 0). Patients could have a maximum index score of 6 (all marker concentrations are high, except TRAIL) or a minimum of 0 (all marker concentrations are low, except TRAIL). The study found that patients with an index of 4 or more should be treated with only single-agent sorafenib, whereas patients with an index of less than 4 should be treated with combination therapy. The study findings supported the hypotheses that broad plasma profiling of CAFs may be a practical approach for identifying predictive biomarkers for therapies in RCC, that exploratory analysis did in fact identify individual CAFs before treatment that correlated with PFS and biologic activity, and that a 6-CAF signature at baseline appears to have greater predictive power than individual markers for treatment selection.

Acquired Resistance to VEGFR Blockade

Also at the KCA meeting, Dr. Michael Atkins discussed the many potential pathways for the development of acquired resistance to VEGFR blockade. He explained in his presentation that in many tumors, the development of resistance to a targeted therapy is due to a mutation in the receptor or tumor, but this is usually not the case in kidney cancer. In patients with kidney cancer, the mechanism of acquired resistance appears to be due to restoration of angiogenesis through incomplete blockade of the VEGF pathway, increased pericyte coverage of tumor blood vessels, recruitment of marrow-derived pro-angiogenic

cells, induction of VEGF independent pathways, proangiogenic changes in the stroma, and loss of endogenous angiostatic pathways; and enhanced tumor invasiveness. Although the optimal treatment is uncertain, approaches have included adjustments in the dose or schedule of the tyrosine kinase inhibitor (TKI), switching to a different TKI or mTOR inhibitor, or the addition of bevacizumb (Avastin, Genentech) or an mTOR inhibitor to TKI therapy.

Dr. Atkins explained 3 different tumor lines identified in animal models—786-O (HIF2 only tumor), A498 (HIF1/HIF2 tumor), and CAKI-1 (VHL wild type)—which show 3 different patterns of response and resistance to sorafenib. In CAKI-1 tumor lines, the resistance starts from baseline. In 786-O tumor lines, tumor growth after sorafenib resistance is sufficiently accelerated to outpace control tumors, but this effect is somewhat ameliorated by higher doses of sorafenib.

In one experiment, resistance to sorafenib appeared to be reversible. This finding led investigators to examine whether a break in therapy might restore sensitivity to treatment. In a preliminary study that compared continuous therapy with intermittent therapy (3 days on treatment followed by 4 days off treatment), the time it took for a tumor to grow to 20 mm was delayed in the intermittent therapy group.

In human imaging studies, higher baseline perfusion corresponded to better response to therapy, and changes in perfusion at 1 month were better predictors of response than tumor size. In one study, perfusion started to return 3 weeks before the tumor started to grow, suggesting that arterial spin labeling imaging may help provide a model to understand resistance.

Resistance has been associated with upregulation of peptide growth factor, sphingosine kinase, calvasculin, chemokine CXC motif receptor 4, arginase II, hypoxiainducible protein 2, and VEGF. Interferon a-regulated genes are downregulated in patients with acquired resistance. The top upregulated genes are matrix metalloproteinase 1, stearoyl-coa desaturase, calvasculin (metastasin), arginase II placental growth factor, and sphingosine kinase. In murine models, the plasma factors associated with angiogenic escape include increased Interleukin-8 and decreased IP-10. In renal cell carcinoma patients, these factors include increased arginase and increased angiopoeitin 2.

Dr. Atkins concluded that further studies of patients with acquired resistance to VEGFR blockade should employ a treatment regimen in which an additional agent is added at the earliest sign of resistance and combination therapy is compared to treatment with a TKI alone. Endpoints should include changes in perfusion, changes in the plasma cytokine panel, and increases in PFS.