KIDNEY CANCER UPDATE

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The Year in Review in Kidney Cancer

Based on a presentation by Toni K. Choueiri, MD, at the ASCO Genitourinary Cancers Symposium

There were no major changes in the therapeutic landscape for metastatic renal cell carcinoma (RCC) in 2014, according to Toni K. Choueiri, MD. A review of more than a thousand studies by Dr Choueiri and his colleagues, however, revealed "a lot of publications that provided important insights for future trials and management of patients."

Dr Choueiri, who is an associate professor of medicine at Harvard Medical School in Boston, Massachusetts, made his remarks during the Year in Review address at the 2015 Genitourinary Cancers Symposium of the American Society of Clinical Oncology (ASCO) in Orlando, Florida. His talk addressed existing targeted agents, health outcomes research, biomarkers, emerging targets, and non–clear cell RCC.

Studies of Targeted Agents

As confirmed by the most recent RCC guidelines from the National Comprehensive Cancer Network, which were published in early 2015, there have been no major changes in the treatment of metastatic RCC in the past year.[1] However, Dr Choueiri highlighted 3 trials of targeted agents that produced particularly valuable information in 2014.

The first study was an updated report from the COMPARZ trial of frontline targeted therapy using vascular endothelial growth factor receptor (VEGFR) inhibitors for patients with metastatic RCC. This study, which at this time is the largest trial of targeted therapy in the advanced RCC setting, found that pazopanib (Votrient, GlaxoSmithKline) is noninferior to sunitinib (Sutent, Pfizer) in the frontline setting. As reported by Motzer and colleagues, the median overall survival (OS) was 28.3 months with pazopanib and 29.1 months with sunitinib (P=.24).[2] Dr Choueiri explained that this is important because it "provides a benchmark for future trials of single-agent pazopanib or sunitinib as the control arm in the frontline setting."

The second study was the INTORSECT trial by Hutson and colleagues, which compared the VEGFR tyrosine kinase inhibitor (TKI) sorafenib (Nexavar, Bayer/Onyx) and the mammalian target of rapamycin (mTOR) inhibitor temsirolimus (Torisel, Wyeth) as second-line agents for metastatic RCC that had progressed on sunitinib.[3] This study found no difference in median progression-free survival (PFS) between the groups: 4.28 months for temsirolimus and 3.91 months for sorafenib (P=.19). In contrast, the median OS—a secondary endpoint—was longer with sorafenib than with temsirolimus (16.64 vs 12.27 months; P=.01). Dr Choueiri, who was "puzzled by the result," said he was unable to fully explain why sorafenib would lead to better OS but not PFS in this study, especially given that patients had similar baseline characteristics and had received third-line therapies in similar proportions in both arms.

The third study was RECORD-3 by Motzer and colleagues,[4] which was first presented at the annual meeting of ASCO in 2013. This large, randomized, phase 2 study compared a standard sequence of sunitinib followed by everolimus (Afinitor, Novartis) vs everolimus followed by sunitinib for patients with metastatic RCC. PFS was better in the sunitinib-first group in patients with good-risk, poor-risk, and non–clear cell RCC (hazard ratios, 1.2, 1.7, and 1.5, respectively). OS also was better in the sunitinib-first group (hazard ratio, 1.24). "Therefore, starting with a VEGF TKI remains standard," said Dr Choueiri.

Health Outcomes Research

Dr Choueiri also presented results from health outcomes research in RCC. One of the reports he highlighted was a study by Heng and colleagues[5] that examined real-world outcomes of patients with metastatic RCC. The researchers found that when commonly used trial inclusion and exclusion criteria were applied to patients in the International Metastatic RCC Database Consortium (IMDC), 35% of the patients were ineligible. Furthermore, these ineligible patients had a significantly worse response rate to targeted therapy, a shorter median PFS, and a shorter OS compared with eligible patients. "Level 1 evidence vs actual practice are not always in sync," said Dr Choueiri.

Another study, by Ko and colleagues,[6] found that the IMDC prognostic model could be applied to patients

previously treated with targeted therapy who were undergoing second-line therapy.

An additional study based on the IMDC found that most patients benefited from tumor removal, except for those with at least 4 of the 6 IMDC risk factors: anemia, thrombocytosis, neutrophilia, Karnofsky performance status less than 80, and less than 1 year from diagnosis to first-line targeted therapy. "You need to remember these 6 risk factors," Dr Choueiri emphasized. This study, by the IMDC, was published in *European Urology*.[7]

Dr Choueiri also highlighted work by McKay and colleagues[8] on the effect of angiotensin system inhibitors (ASIs) in metastatic RCC. This study found that OS improved in patients who received both a VEGFR-targeting therapy plus an ASI, but not with other anticancer agents such as mTOR inhibitors or interferon-α. Similarly, when the antihypertensive used with the VEGFR-targeting therapy was not an ASI (eg, β-blocker, calcium channel blocker), there was no improvement in OS.[8]

Biomarkers

"Biomarkers are an area dear to my heart," said Dr Choueiri, who began by discussing the use of biomarkers in early-stage RCC. He pointed to his own work, published by Schutz and colleagues in 2012, which found that patients with localized RCC and the *MET* polymorphism rs11762213 might have an increased risk of recurrence after nephrectomy.[9] Hakimi and colleagues[10] validated this finding in a large group of patients from The Cancer Genome Atlas (TCGA); these results were presented at the ASCO Genitourinary Cancer Symposium in 2014.

Also in 2014, Escudier and colleagues[11] presented findings that a 16-gene recurrence score was able to predict the risk of recurrence in patients with early-stage RCC after adjustment for conventional clinical measures. This study validated findings from an earlier presentation by Dr Brian Rini.[12]

Dr Choueiri said the bigger need is for biomarkers to predict response to cytokines, VEGFR-targeted drugs, and mTOR inhibitors in patients with metastatic disease. Although none of these biomarkers are ready for use at this time, 3 important studies were published last year. In the first study, by McDermott and colleagues,[13] patients with metastatic RCC with who were considered "good risk" based on clear-cell histology subclassification and carbonic anhydrase-9 immunohistochemical staining were no more likely to respond to high-dose interleukin 2 than those considered to be "poor risk."

In the second study, with Dr Choueiri as the first author,[14] elevated levels of tumor cell programmed death ligand 1 (PD-L1) and elevated levels of PD-L1 plus tumor CD8+ T-cell counts were both associated with shorter survival in patients with metastatic RCC who received the VEGFR-targeted agents pazopanib or sunitinib.

The third report, which Dr Choueiri said might be the most clinically relevant right now, found that alterations in 2 genes (*TSC1* and *MTOR*) were associated with exceptional responses to rapamycin and its analogues, which is usually rare in an unselected population.[15]

Emerging Targets

Dr Choueiri briefly discussed emerging targets in RCC, including the programmed death 1 (PD-1)/PD-L1 pathway, and recommended an article by Harshman and colleagues for a more-detailed examination.[16] He discussed a study that he presented at the ASCO and European Society of Medical Oncology (ESMO) annual meetings in 2014 that examined what happens in the body when patients receive nivolumab (Opdivo, Bristol-Myers Squibb). He found that from the baseline to the eighth day of cycle 2, the number of CD3+ cells increased by 78% and the number of CD8+ cells increased by 88%.[17]

Another important study was the one published by Motzer and colleagues in which 3 doses of nivolumab were tested in 168 patients with metastatic RCC. The median PFS, a primary endpoint, was "a bit disappointing," but the objective response rate was 20% and the median OS was "certainly very encouraging"—from 18.2 to 25.5 months, vs the 15 to 16 months reported with everolimus or axitinib (Inlyta, Pfizer). OS may be the critical endpoint in studies of PD-1 inhibitors, he explained.

Dr Choueiri said that his enthusiasm for a biomarker for single-agent PD-L1 therapy dampened a bit after the initial report from Dr Suzanne Topalian. After this initial report, several larger studies dedicated to metastatic RCC showed that even patients with negative PD-L1 status can respond to a PD-1 or a PD-L1 inhibitor. He emphasized that the biggest problem with testing for PD-L1 is the lack of standardization of the immunohistochemical assay. "The tumor, the immune cell, and even the criteria for positivity are different" from agent to agent.

Other studies have begun to look at PD-1 inhibitors in combination with other agents. A phase 1 study by Amin and colleagues[18] looked at nivolumab in combination with the VEGFR TKIs, and another phase 1 study by Hammers and colleagues[19] looked at nivolumab with the immune checkpoint inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb). Most of the patients were pretreated in both of these studies. The PFS and response rate were encouraging, but grade 3 and 4 toxicities were as high as 81%. "We definitely need to be cautious in proceeding," said Dr Choueiri. The group with the lowest grade 3 and 4 toxicity (29%) was the nivolumab plus low-dose ipilimumab group.

Non–Clear Cell RCC

A large amount of data on non–clear cell RCC was published in 2014. One study of note was on chromophobe RCC by Davis and colleagues for the TCGA Research Network.[20] This study looked at several molecular platforms, from whole exome sequencing to DNA methylation. The researchers found that mitochondrial DNA is essential to disease biology and that there is some upregulation of telomerase reverse transcriptase, which is involved in DNA repair. However, overall there is low rate of mutation of cancer-relevant genes.

Another "very important" study, which was presented by Dr Nizar Tannir at the 2014 ASCO annual meeting,[21] randomly assigned 73 patients with non–clear cell RCC to receive either everolimus or sunitinib. The researchers found no difference in PFS between sunitinib and everolimus, but an interim analysis showed a benefit in OS with sunitinib, so the trial was stopped early. There was also a trend toward better OS in patients without sarcomatoid histology. "I want to congratulate Dr Tannir and the group at MD Anderson" for conducting this trial, Dr Choueiri said.

Dr Choueiri said that many of his patients with non–clear cell RCC are ineligible for clinical trials of PD-1/PD-L1 inhibitors because these tumors are less studied than their clear-cell counterparts. This practice should change, however. According to his own study[22] of more than 100 patients with non–clear cell RCC, patients can be positive for the PD-L1 biomarker.

Conclusion

Dr Choueiri concluded by saying that there were no major changes overall in the RCC therapeutic landscape in 2014. He said he was "very happy with the external validation of 2 signatures in localized RCC" but cautioned the audience about PD-L1 positivity, which is associated with a worse response to VEGFR TKIs and a better response to single-agent nivolumab.

Immune checkpoint blockers and drugs that target acquired mechanisms of resistance to VEGFR inhibitors are promising, he said. He also pointed out that much work remains to be done in non–clear cell RCC.

"Finally, I want to highlight the importance of our patients," he said. "I firmly believe they deserve a cure."

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