Sequencing Therapies in Renal Cell Carcinoma

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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With dual checkpoint inhibition, immunotherapy and vascular endothelial growth factor (VEGF)–inhibitor combinations, and tyrosine kinase inhibitor monotherapy all viable options for advanced renal cell carcinoma, choosing the right regimen for patients has become more complicated than ever. At JADPRO Live 2018, Sumanta Kumar Pal, MD, an associate clinical professor at City of Hope Comprehensive Cancer Center, in Duarte, California, discussed how to best utilize immunotherapy in renal cell carcinoma and explained the use of tyrosine kinase inhibitors in the adjuvant setting. Kathleen Burns, AGACNP-BC, OCN®, a nurse practitioner at City of Hope, highlighted some of the potential toxicities and management strategies for various regimens.

NIVOLUMAB AND IPILIMUMAB

As Dr. Pal reported, starting with data presented at the European Society for Medical Oncology 2017 annual meeting, immunotherapy has altered the landscape of advanced renal cell carcinoma. In the CheckMate 214 trial, advanced renal cell carcinoma patients with no prior therapy and reasonable performance status (Karnofsky performance status ≥ 70%) were randomized to nivolumab (Opdivo) and ipilimumab (Yervoy) vs. sunitinib (Sutent), a VEGF inhibitor (Motzer et al., 2018c). Both nivolumab and ipilimumab are immune-based therapies, with nivolumab targeting programmed cell death protein 1 (PD-1) and ipilimumab targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4).

In intermediate and poor-risk patients, said Dr. Pal, the data represent a clear win for dual checkpoint inhibition in terms of overall survival. While the median overall survival was not reached for the nivolumab and ipilimumab combination, it was 26 months with sunitinib. In addition, said Dr. Pal, the overall response rate of 42% with the immunotherapy combination was "pretty outstanding," and the 9% complete response rate for the combination shows that "the cures we've been seeking in the clinic are actually possible."

Nevertheless, said Dr. Pal, there are some caveats to these data. For patients who are not intermediate or poor risk, sunitinib in fact outperforms nivolumab and ipilimumab. The response rate is approximately

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doubled with sunitinib as compared to the response rate with the immunotherapies.

"If you have a patient who is considered at good risk, they should probably still get a VEGF inhibitor in this setting," said Dr. Pal.

IMMUNOTHERAPY-RELATED TOXICITY

Despite the high rate of response, given the toxicities associated with dual checkpoint inhibition, Dr. Pal cautioned that a highly skilled multidisciplinary team is essential for administering this regimen.

"We always think about immunotherapy as maybe being a kinder, gentler approach for patients, but about a quarter of patients actually discontinued nivolumab and ipilimumab on account of drug toxicity, which is double the number of patients that discontinued sunitinib due to toxicity," said Dr. Pal. "This is definitely not the kinder and gentler approach that we were hoping for."

Approximately 46% of patients on nivolumab and ipilimumab experienced grade 3 to 4 adverse events, including a high incidence of fatigue, diarrhea, pruritis, and hypothyroidism. Also to bear in mind, said Dr. Pal, was that about 60% of patients receiving the combination need to consider steroid therapy at some point during their treatment.

"I am personally pretty heavy-handed in using steroids in this population in the clinic," Dr. Pal observed.

Finally, for clinicians on the fence about whether this combination is right for a patient, said Dr. Pal, testing for programmed cell death ligand 1 (PD-L1) status could potentially be helpful, as patients who tested positive for the biomarker showed a tremendous difference in progression-free survival.

With respect to steroid treatment, Ms. Burns emphasized that the use of steroids has demonstrated no effect on immunotherapy response, so it is important to let patients know that their treatment may not be compromised. In addition, Ms. Burns noted that endocrine and thyroid adverse events are the only class that do not require steroids. For steroid dosing more than 20 mg/day over four weeks, said Ms. Burns, prophylaxis for pneumonia is recommended, and for 6 to 8 weeks, patients should receive prophylaxis for fungal infections.

BEVACIZUMAB AND ATEZOLIZUMAB

In a similar patient population to CheckMate 214, patients with advanced renal cell carcinoma with no prior history (except clear cell or sarcomatoid histology) were randomized to monoclonal antibodies bevacizumab (Avastin) and atezolizumab (Tecentriq) vs. sunitinib in a phase III study (Motzer et al., 2018b). As Dr. Pal explained, sarcomatoid features are aggressive and tend to indicate poor prognosis.

In PD-L1–positive patients, investigators observed significant improvement in progression-free survival, which was the study's primary endpoint (7.7 months with sunitinib vs. 11.2 months with the combination of bevacizumab and atezolizumab). As Dr. Pal reported, response rates were also higher with bevacizumab and atezolizumab (43%) than with sunitinib (35%).

"What really stood out, however, is the complete response rate of approximately 9%," said Dr. Pal, who noted that with independent assessment the rate was closer to 15%. "Many of the responses we're seeing with bevacizumab and atezolizumab are pretty durable, and these rates are certainly much higher than one would typically anticipate with drugs like sunitinib in years past."

Overall survival also showed a trend towards improvement, Dr. Pal noted.

EXCEPTIONAL TOLERABILITY

Regardless of how overall survival pans out, said Dr. Pal, what really stands out about the combination of bevacizumab and atezolizumab is the exceptional tolerability. Furthermore, when compared to the combination of nivolumab and ipilimumab, steroid utilization dropped from 60% to only 16%.

As Ms. Burns reported, a 91-year-old patient showed a durable response with bevacizumab and atezolizumab for over 3 years with only varying degrees of fatigue and proteinuria.

"It's important to include older adults in our clinical trials and not be afraid of treating them, but we must pay exquisite attention to their quality of life and symptomology," said Ms. Burns.

"With all of the various regimens available, the regimen of bevacizumab and atezolizumab is incredibly well tolerated in older patients," Dr. Pal added. "It hasn't achieved regulatory approval yet,

but I'm keeping my fingers crossed, and it would be one of my preferred choices for the frail patient."

AXITINIB AND AVELUMAB

As Dr. Pal reported, several different trials looking at combinations of small molecule tyrosine kinase inhibitors or other VEGF inhibitors with immunotherapy have demonstrated complete response plus partial response rates between 40% and 50%, and clinical benefit rates suggest that nearly 100% of patients are deriving benefit from these therapies.

More recently, the combination of axitinib and avelumab (Bavencio) vs. sunitinib at standard dosing showed a marked extension in terms of progression-free survival in PD-L1–positive patients (13.2 vs. 7.2 months; Motzer et al., 2018a). The overall population showed a similarly dramatic benefit in progression-free survival in patients receiving axitinib and avelumab vs. those receiving sunitinib (13.8 months vs. 8.4 months).

"These are very compelling data," said Dr. Pal, who also pointed out an early trend in improved overall survival.

In terms of treatment-related adverse events, however, Dr. Pal emphasized that "Axitinib has a fairly significant side-effect profile associated with it, including diarrhea, hypertension, and hand-foot syndrome, among other adverse events."

Although comparable to other immune-based regimens, avelumab is also associated with the "typical array" of immune-related adverse events. The total frequency of immune-related adverse events is around 38%, said Dr. Pal, which includes incidences of colitis and liver-related toxicity.

"One of the more unusual side effects we've observed with this immunotherapy was myasthenia gravis, which is an autoimmune disorder of the proteins in the postsynaptic membrane of the neuromuscular junction," said Ms. Burns. "Presenting symptoms can be weakness, eye droop, and intermittent muscle weakness. This patient had the drug withheld and showed marked improvement in his symptoms following treatment with physostigmine."

TYROSINE KINASE INHIBITOR MONOTHERAPY

Despite the availability of several, exciting, new regimens, said Dr. Pal, there is still going to be a role for the use of tyrosine kinase inhibitor monotherapy for a subset of patients. CABOSUN, a randomized clinical trial, looked at cabozantinib (Cabometyx), an oral tyrosine kinase inhibitor that targets two VEGF receptors (MET and AXL), vs. sunitinib (Choueiri et al., 2018). As Dr. Pal reported, in an intermediate and poor-risk population of patients with advanced renal cell carcinoma, cabozantinib demonstrated a significant improvement in progression-free survival as compared to that seen with sunitinib (8.6 months vs. 5.3 months).

"With all these newer regimens at our disposal, the benefit of cabozantinib really holds in individuals who have bone metastases, which is something we don't necessarily see with other available agents," said Dr. Pal. "Cabozantinib, which I'm convinced is probably the best VEGF inhibitor that we have to date, still represents a very reasonable option in the front-line setting for our patients."

Finally, with respect to managing toxicities, Ms. Burns underscored the importance of patient and family education and feedback.

"As I work with these drugs, I've learned to help patients understand that dose reduction is not a failure on their part at all, but a part of treatments," said Ms. Burns. "I've also learned that the management and support of patients who are on oral therapies can be at least as challenging as intravenous treatment."

Disclosure

Dr. Pal has consulted with Astellas, Aveo, Bristol-Myers Squibb, Eisai, Exelixis, Genentech, Ipsen Novartis, Pfizer, and Roche. Ms. Burns has served on speakers bureaus for Amgen, Astellas, and Pfizer.

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