KIDNEY CANCER UPDATE

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Clinical Use of Checkpoint Inhibition in Kidney Cancer

Based on a presentation by Hans J. Hammers, MD, PhD, at the ASCO Genitourinary Cancers Symposium

A "plethora of agents" to inhibit programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) are in clinical development for kidney cancer and other cancers, according to Hans J. Hammers, MD, PhD.

"Time will tell how we use these drugs" in kidney cancer, said Dr Hammers, who recently joined the Kidney Cancer Program at UT Southwestern in Houston, Texas, as an associate professor. He made his remarks during the clinical half of the renal cancer keynote lecture at the 2016 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, held in San Francisco, California. He discussed results from CheckMate 025 (Study of Nivolumab vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma) and from studies of combination immunotherapy, including CheckMate 016 (Nivolumab in Combination With Sunitinib, Pazopanib, or Ipilimumab in Subjects With Metastatic Renal Cell Carcinoma).

CheckMate 025

CheckMate 025 is the phase 3 trial that led to the approval of nivolumab (Opdivo, Bristol-Myers Squibb) for use in patients with kidney cancer who had received prior treatment with a tyrosine kinase inhibitor (TKI). Dr Hammers pointed to data that Padmanee Sharma presented at the 2015 European Society for Medical Oncology (ESMO) annual meeting, which were simultaneously published by Motzer and colleagues.[1] In this trial, researchers randomly assigned 821 patients with advanced clear cell kidney cancer who had received prior treatment to either nivolumab 3 mg/kg intravenously every 2 weeks or everolimus (Afinitor, Novartis) 10 mg orally per day.

The population was "well balanced" and reflected the classic patient population with kidney cancer, which is male predominant. Approximately half the patients were in the intermediate category of the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk group, one-third were in the favorable-risk category, and 15% were in the poor-risk category. Most of the patients had received 1 prior antiangiogenic regimen. The majority of patients were from the United States and Western Europe.

Dr Hammers said that "nobody really wants to start with" the slide from CheckMate 025 that shows progression-free survival (PFS), which was not the primary endpoint of the study. "But I think it's important to start with this one," he said, because it expresses the clinical reality that most patients' tumors continue to progress after immunotherapy treatment begins. In Checkmate 025, the Kaplan-Meier curves for median PFS are nearly identical for nivolumab and everolimus until month 9, at which time the response to nivolumab begins to pick up and a tail appears on the curve. If median PFS had been the primary endpoint, this would have been a negative study.

Fortunately, immunotherapy "tends to surprise us." In this case, nivolumab improved overall survival from 19.6 months to 25.0 months (P=.0018), which led to its "speedy approval" for use in kidney cancer. What remains to be determined is whether this agent improves long-term survival, an outcome not captured by the measurement of median overall survival. Regulatory agencies should consider adding a measure of long-term survival or long-term PFS to their requirements for immunotherapy agents, Dr Hammers said.

Nivolumab was associated with a benefit in virtually all of the core subgroups, including those stratified by MSKCC prognostic risk group, use of prior antiangiogenic agents, sex, and age. Although median overall survival was not higher with nivolumab than with everolimus in patients aged 75 and older, Dr Hammers said he has treated many patients in their 80s who are doing well on nivolumab.

Although PD-L1 expression is not a predictive marker for response to nivolumab, it is a prognostic marker. Patients whose tumors do not express PD-L1 have a higher median overall survival than those whose tumors do express PD-L1 (27.4 months vs 21.8 months for nivolumab and 21.2 months vs 18.8 months for everolimus).

The objective response rate to nivolumab was 25% in this study, which may not sound high but is "actually quite robust." By comparison, the response rate to everolimus was 5%, and the response rate to axitinib (Inlyta, Pfizer) as second-line therapy in other studies is just 11%.

Most of the responses to nivolumab were partial rather than complete, and other patients experienced

stabilization of their disease. A number of patients had progressive disease as their best response.

The median duration of response was approximately 1 year for patients in both the nivolumab and the everolimus arms. This is high for everolimus, which suggests that the patients in this study were especially sensitive to mammalian target of rapamycin (mTOR) inhibitors. In addition, the treatment was shown to continue benefiting some patients after therapy ended.

Regarding safety, the number of treatment-related adverse events that were grade 3 or 4 was fairly low with nivolumab: just 19%, vs 37% with everolimus. The number of adverse events leading to treatment discontinuations was low with both nivolumab (8%) and everolimus (13%).

Treatment-related adverse events included fatigue, nausea, pruritis, a fairly mild rash, and diarrhea that typically was fairly mild—unlike the diarrhea seen with ipilimumab (Yervoy, Bristol-Myers Squibb). One of the most feared side effects of nivolumab is pneumonitis, which led to several deaths in the early phase of drug development.

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> —Hans Hammers, MD, PhD

Thanks to proper education of patients and physicians, pneumonitis did not cause any deaths in this trial.

Another very important endpoint is quality-of-life scores on the Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS), which improved from baseline for patients on nivolumab but not for patients on everolimus. Dr Hammers said that in his opinion, everolimus is better tolerated than TKIs. "So to do better than that is actually quite significant, and speaks to the tolerability of this agent."

Dr Hammers said that it is important for oncologists to be aware that immunotherapy also may cause type 1 diabetes, rheumatoid arthritis, encephalitis, and other rare autoimmune phenomena. "When in doubt, you just start steroids, and most of the time the patient improves quite nicely."

Immunotherapy also may lead to tumor flare, in which infiltration of the tumor creates the appearance of progressive disease on computed tomography but actually reflects a transient inflammatory state. Based on data from a phase 2 dose-ranging study that Saby George presented at the 2015 ESMO annual meeting, approximately 20% of patients may benefit from continuing treatment with immunotherapy.[2]

Dr Hammers described the case of a 74-year-old woman with mostly mediastinal lymph node–based disease who previously had been treated with pazopanib (Votrient, Novartis) and achieved a partial response within 6 months. After 1.5 years on nivolumab, she showed progressive disease with an enhancing nodule in the intestine. At around this time, she also developed a new brain lesion and started to experience partial seizures.

After the patient died of complications from surgery to resect the brain lesion, a rapid autopsy revealed that the mediastinal lymph node was essentially free of tumor at the time of her death, but renal cell carcinoma cells were present in the intestinal lesion and in the brain lesion. The primary tumor was highly positive for PD-L1 expression and had associated infiltration of CD8 cells, whereas the intestinal lesion and the brain lesion had a loss of PD-L1 expression and few infiltrating T lymphocytes. This suggests that the immunologic state of the tumor might evolve after late recurrences or relapses.

Immunotherapy in Combination

Given that checkpoint inhibitors work well on their own, is there a role for combining 2 of them? A combination of the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) ipilimumab and the PD-1/PD-L1 inhibitor nivolumab has been approved for use in melanoma. CTLA-4 is believed to play a greater role in the primary lymph node organs, whereas PD-1 appears to be more important in the effector phase in the tumor microenvironment. A combination of the two has produced some very exciting data in melanoma, and we saw the same in metastatic renal cell carcinoma in the CheckMate 016 study.[3] This study adopted the dosing schema from the melanoma study: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg vs nivolumab 1 mg/kg plus ipilimumab 3 mg/kg.

Nearly 100 patients were treated in this trial. The overall response rate was 38% in the first group and 43% in the second group, which is somewhat unprecedented in renal cell carcinoma. Importantly, the responses were durable. Some patients who halted treatment—primarily because of toxicity—continued to respond and needed no further treatment.

Although efficacy was fairly comparable between the 2 regimens, the toxicity was markedly different: grade 3 or 4 toxicities occurred in 34.0% of the patients on the higher dose of nivolumab and lower dose of ipilimumab, and in 63.8% of the patients on the lower dose of nivolumab and the higher dose of ipilimumab. Among the 6 patients who received a higher dose of both nivolumab and ipilimumab (3 mg/kg of each), all required corticosteroids. This high-dose regimen was abandoned.

Combinations With VEGF Pathway Inhibitors

Combinations of immunotherapy and vascular endothelial growth factor (VEGF) pathway inhibitors are logical because kidney cancer is a "VEGF-addicted disease." The same study that examined the combination of nivolumab and ipilimumab in kidney cancer also tested the combination of nivolumab with either sunitinib (Sutent, Pfizer) or pazopanib as second-line treatment. Patients who had been treated with pazopanib received nivolumab/sunitinib, and those who had been treated with sunitinib received nivolumab/pazopanib. During the dose escalation phase, an early sign of liver toxicity occurred in the pazopanib arm, and this arm was halted.

Dose escalation was successful in the sunitinib arm, which was expanded to include untreated patients. The overall response rate was "quite impressive" with both regimens: 52% in the nivolumab/sunitinib group, in which half the patients were treatment-naive, and 45% in the nivolumab/pazopanib group, in which all the patients were pretreated.

Both combinations were associated with liver toxicity, however. This toxicity led to early termination of the pazopanib arm, and the toxicity rate with sunitinib eventually caught up. Rates of grade 3/4 toxicities were higher in this combination trial than in trials of single-agent therapy.

Regarding the more selective VEGF pathway inhibitors, in 2014 David McDermott presented some data from a phase 1b trial that combined the PD-L1 inhibitor atezolizumab (Tecentriq, Roche) with bevacizumab (Avastin, Genentech).[4] Good early results and tolerability led to a large trial in which patients were randomly assigned to an atezolizumab-alone arm, an atezolizumab/bevacizumab arm, or a sunitinib-alone arm (NCT01984242). Patients had the option to cross over to combination therapy if their disease progressed on monotherapy. "This is a very exciting study that we're looking forward to hearing about later this year," said Dr Hammers.

Toni Choueiri presented some preliminary data at the 2015 annual meeting of the Kidney Cancer Association on combining axitinib plus pembrolizumab (Keytruda, Merck) in a group of 11 treatment-naive patients with advanced renal cell carcinoma.[5] This regimen was reasonably well tolerated, with just one grade 3 liver function test elevation. The overall response rate was 55%, which Dr Hammers said was "exciting."

Dr Hammers cautioned that although comparing results from 3 different preliminary studies is problematic, a response lasting 2 years occurs in approximately 10% of patients taking a PD-1 inhibitor alone, 10% of patients taking a PD-1 inhibitor plus a TKI, and 20% of patients taking a PD-1 inhibitor plus a CTLA-4 inhibitor. "These are some interesting preliminary data," he said. Looking at more than just objective response rate and PFS to comprehensively understand these agents "is going to be important."

The phase 3 trials that are going to transform first-line therapy are (1) nivolumab/ipilimumab vs sunitinib, which has fully accrued—"we hope to learn the results in 2018"; (2) atezolizumab/bevacizumab vs sunitinib; (3) avelumab/axitinib vs sunitinib, which is ongoing; and (4) pembrolizumab/axitinib vs sunitinib, which is still in the planning stages.

Conclusion

In summary, nivolumab produces a clear overall survival benefit that occurs even in patients who do not respond. "Just the exposure to the PD-1 inhibitor can make patients live longer," said Dr Hammers. In addition, PD-1/PD-L1 inhibitors have a potential for durable responses. Finally, these agents are remarkably well tolerated and have beneficial effects on quality of life when used as single agents. "They are certainly disrupting the current treatment paradigms," he said, which traditionally have called for a TKI followed by another TKI or by an mTOR inhibitor.

PD-1/PD-L1 inhibitors clearly are going to be the backbone for future combination therapies. In the meantime, "more mundane questions" remain. For example, what is the optimal schedule—should these agents be given every 2 weeks, or is every 3 or 4 weeks sufficient? Another example is, how long do we need to treat? Should patients receive these agents for 2 years, for 1 year, or for 6 months? These are all interesting questions that should be answered.

References

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