

BLADDER CANCER IN FOCUS

Current Developments in Bladder Cancer Research

New Treatments for Patients With Progressive Metastatic Urothelial Carcinoma



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H&O Does urothelial carcinoma pose any challenges or opportunities for the development of new drugs?

JR Urothelial carcinoma tends to affect older patients, who often have comorbidities that complicate treatment. The average age of patients with urothelial cancer at diagnosis is 73 years. Among these older patients, organ function may not be adequate for certain therapies, particularly cisplatin. Urothelial carcinoma is a tobacco-related illness, so patients often have vascular disease and pulmonary disease, which can make treatment challenging.

Urothelial carcinoma is characterized by many genomic alterations and mutations in several druggable oncogenes. There is concern that the high mutation burden means that some of the mutations may be just passengers; they are not necessarily oncogenic for the tumor. However, some of these mutations represent an opportunity for treatment. In addition, the tumor is known to be immunogenic. Bacillus Calmette-Guérin is a well-established intravesical therapy for non-muscle invasive bladder cancer. This long history has provided the rationale for testing immune checkpoint drugs in urothelial carcinoma. The high mutation burden, which might be a downside for targeted therapy, is advantageous for immunotherapy because it provides more neoantigens for the immune system to recognize, increasing the chance for tumor response. There are many opportunities to develop novel immunotherapies and immunotherapy combinations with standard therapies. However, the standard chemotherapies we use have not synergized well with immunotherapy when given simultaneously.

H&O What have recent studies in urothelial carcinoma shown?

JR Platinum-based chemotherapy is the standard first-

line therapy for patients with metastatic urothelial cancer. Recent trials have evaluated immunotherapy with or without chemotherapy, some with negative results.

The KEYNOTE-361 trial evaluated 3 arms: pembrolizumab (Keytruda, Merck) plus chemotherapy, pembrolizumab alone, and chemotherapy alone. A presentation at the 2020 European Society for Medical Oncology (ESMO) virtual congress showed no convincing improvement in outcomes with the addition of immunotherapy to chemotherapy vs chemotherapy alone. The DANUBE trial compared durvalumab (Imfinzi, AstraZeneca) monotherapy, durvalumab plus tremelimumab, and chemotherapy. There was no improvement in survival in either of the experimental arms. An interesting finding, however, was that the combination of durvalumab plus tremelimumab—the programmed death ligand 1 (PD-L1)/cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) arm—improved survival among patients with high expression of PD-L1, a secondary endpoint.

The IMvigor130 trial evaluated the addition of atezolizumab (Tecentriq, Genentech) to gemcitabine/cisplatin. Progression-free survival was improved among patients treated with atezolizumab, gemcitabine, and cisplatin vs gemcitabine and cisplatin alone, although the difference was not clinically meaningful. This finding did not impact clinical practice. The data for overall survival are not yet mature.

The plenary session at the 2020 American Society of Clinical Oncology meeting included a report on the JAVELIN Bladder 100 study, which compared avelumab (Bavencio, EMD Serono/Pfizer) maintenance therapy vs observation. The trial enrolled patients previously treated with chemotherapy who experienced a partial or complete response or stable disease. The addition of avelumab maintenance led to a robust benefit, with an improvement in survival of more than 7 months. Therefore, the standard treatment for the first-line therapy of patients with urothelial cancer is platinum chemotherapy followed by immunotherapy. If patients develop progressive disease

during treatment with chemotherapy, they usually receive pembrolizumab. If they do not progress during treatment with chemotherapy, they receive avelumab maintenance.

H&O What are the newer options for patients with progressive disease?

JR There has been no standard of care for patients with progressive disease after immunotherapy. There are now 2 options in the postplatinum and postimmunotherapy setting: erdafitinib (Balversa, Janssen) and enfortumab vedotin-ejfv (Padcev, Astellas/Seattle Genetics). Each of these treatments has the potential to be very effective for some patients, although the toxicity burden can sometimes be high. The immunotherapy agents tend to be better tolerated, but the rate of response is typically lower, with lower response rates but more durable remissions.

The US Food and Drug Administration (FDA) granted accelerated approval to enfortumab vedotin-ejfv in December 2019 based on the phase 2 EV-201 trial. The phase 1 trial, EV-101, was a dose-escalation study that reached a dose of 1.25 mg/kg on days 1, 8, and 15 every 28 days. The maximum tolerated dose was not reached. However, based on pharmacokinetics and toxicity, the researchers decided to stop escalation at the dose of 1.25 mg/kg. Data from the phase 1 trial suggested that enfortumab vedotin-ejfv was highly active.

Previously, effective treatments were lacking for patients who develop progressive disease during chemotherapy or immunotherapy. Third-line options such as chemotherapy (taxanes, or [if in Europe] vinflunine) were perceived as suboptimal. This setting therefore represented a major unmet need. Data from studies of enfortumab vedotin-ejfv and erdafitinib showed that these tumors can still respond to treatment and that patients might benefit.

H&O What type of drug is enfortumab vedotin-ejfv?

JR Enfortumab vedotin-ejfv is an antibody-drug conjugate. It is a fully humanized monoclonal antibody that targets nectin-4, a cell-surface protein that is involved in cell-cell adhesion. Nectin-4 is highly expressed in bladder cancer. It also has some expression in the skin, which is a source of potential toxicity for the drug. The nectin-4 antibody is conjugated via a protease-cleavable linker to monomethyl auristatin E (MMAE), which is a potent cytotoxic. Enfortumab vedotin-ejfv is an antimicrotubule agent, so when the antibody-drug conjugate is administered intravenously, the antibody portion binds to the tumor cell surface nectin-4, and then becomes internalized. The MMAE is released inside the cell, where it attacks the microtubules, leading to apoptosis

and cell death. To patients, I describe the drug as almost a targeted chemotherapy, in that it selectively delivers the cytotoxic directly to the site of the cancer cells. Enfortumab vedotin-ejfv is a targeted therapy that takes advantage of the high levels of expression of nectin-4 in patients with urothelial carcinoma.

H&O What were the findings from the phase 2 EV-201 trial?

JR EV-201 was a single-arm, open-label trial that evaluated enfortumab vedotin-ejfv in 125 patients who had received prior platinum-based chemotherapy and immunotherapy with either a programmed death 1 (PD-1) inhibitor or a PD-L1 inhibitor. The objective response rate was 44% (95% CI, 35.1%-53.2%), which is substantially higher than the rate of 10% to 20% typically expected with third-line therapy, such as paclitaxel or docetaxel. The complete response rate was 12%. The median duration of response was 7.6 months (range, 0.95-11.30+ months). The median overall survival was approximately 1 year, compared with a range of 6 to 9 months for the typical third-line agents.

The high response rates and favorable survival data led the FDA to grant accelerated approval to enfortumab vedotin-ejfv. Full approval is pending per the results of a confirmatory trial. A recent press release reported results of EV-301, which is the randomized phase 3 trial of enfortumab vedotin-ejfv vs the investigator's choice of intravenous docetaxel, paclitaxel, or vinflunine (in the European Union only). The data showed that enfortumab vedotin-ejfv improved overall survival (HR, 0.70; 95% CI, 0.56-0.89; $P=.001$) and progression-free survival (HR, 0.61; 95% CI, 0.50-0.75; $P<.00001$) compared with the standard chemotherapies. Based on the EV-301 trial, I expect that the FDA will convert the accelerated approval to a full approval in this setting. Results should be presented at an upcoming meeting.

H&O What is the toxicity profile?

JR Enfortumab vedotin-ejfv has some of the expected side effects associated with chemotherapy, although rates of hematologic toxicities tend to be lower. MMAE can cause peripheral neuropathy, which is another side effect of enfortumab vedotin-ejfv. In my experience, the peripheral neuropathy is time-dependent: the longer the duration of treatment, the higher the risk of peripheral neuropathy. It can be treatment-limiting in some cases. This toxicity generally improves when the dose of enfortumab vedotin-ejfv is reduced or when administration is suspended or stopped. Patients are frequently able to resume therapy at lower doses after improvement of symptoms.

Skin toxicities are fairly frequent and often occur early in the treatment course. They range from some pruritus to significant rashes and, occasionally, blistering. In very rare cases, a patient develops a severe rash that requires hospitalization. My advice to physicians who prescribe enfortumab vedotin-ejfv is to develop a good relationship with a dermatologist who can help manage the skin toxicity. This toxicity is common, and is an important quality-of-life issue.

A rare but potentially severe side effect of enfortumab vedotin-ejfv is hyperglycemia. The mechanism of action is not yet understood. Approximately 10% of patients developed elevated levels of blood sugars in the phase 2 trial. In most patients, these elevations are not an important concern. A small number of patients, however, will develop very severe and refractory hyperglycemia. The best practice is to check the patient's hemoglobin A1c level before therapy starts. If the glucose levels begin to rise during treatment, the patient should be promptly referred to endocrinology for evaluation. In my experience, the patients most likely to develop severe hyperglycemia are those with a previous diagnosis of diabetes. However, severe cases do occur in patients without diabetes. Hyperglycemia is something to watch for during treatment with enfortumab vedotin-ejfv. Patients with uncontrolled diabetes are poor candidates for enfortumab vedotin-ejfv and probably should not receive it.

H&O Were there any especially notable findings from the EV-201 trial?

JR The 12% complete response rate stood out for me. This rate of complete response is unusual in trials of third-line treatment in bladder cancer. Most treatments do not lead to any complete responses in this setting. The observation that some patients can experience such a dramatic benefit with enfortumab vedotin-ejfv highlights the fact that this agent is very potent against urothelial cancer.

Traditionally, patients with liver metastases have had poor responses to therapy. In the phase 1 and 2 trials of enfortumab vedotin-ejfv, a fairly robust amount of activity was seen in patients with liver metastases compared with what might be expected. Liver metastases have been a poor prognostic feature of second-line and third-line therapy in urothelial cancer. Enfortumab vedotin-ejfv, however, appears to overcome the negative prognostic influence of liver metastases.

H&O Are there patients who are better or worse candidates for this drug?

JR As mentioned, patients with poorly controlled diabetes are poor candidates for enfortumab vedotin-ejfv.

Patients with substantial peripheral neuropathy should not receive enfortumab vedotin-ejfv because they will not be able to remain on treatment.

There is no biomarker available to select patients who will achieve the best response to enfortumab vedotin-ejfv. Nectin-4 is highly expressed in the vast majority of urothelial cancers, and to date, there has been no association found between nectin-4 levels and outcome.

H&O Do you anticipate that the use of enfortumab vedotin-ejfv in urothelial carcinoma will evolve?

JR Enfortumab vedotin-ejfv is being evaluated in combination regimens. I presented results of a study evaluating enfortumab vedotin-ejfv plus pembrolizumab as first-line therapy in patients with untreated metastatic urothelial cancer who were not eligible to receive cisplatin but were candidates for carboplatin. The overall response rate was 73%, which is 15% to 20% higher than would be expected with the best chemotherapy available. The median progression-free survival was approximately a year, which is probably double what would be expected in this patient population. It was not possible to formally estimate overall survival, but the available data appeared to suggest a median overall survival of greater than 1 year. The FDA declared the combination a breakthrough therapy. The regimen is now moving forward into larger clinical trials as first-line therapy for metastatic urothelial cancer patients. Enfortumab vedotin-ejfv is likely to move earlier in the course of the disease, particularly for patients who are not candidates to receive cisplatin-based chemotherapy.

H&O Are there any other promising regimens in development?

JR There are some interesting novel immunotherapy combinations, as well as combinations of fibroblast growth factor receptor (FGFR) inhibitors and immunotherapy. A recent study evaluated FGFR inhibitors in combination with immune checkpoint drugs—erdaftinib with cetrelimab—in patients with cisplatin-ineligible metastatic disease, a population in which immune checkpoint inhibitors might not be expected to work. Preliminary results showed high response rates in a very limited number of patients.

A trial of atezolizumab and rogaratinib, another FGFR inhibitor, showed a 39% response rate in a small cohort of patients. These patients had low levels of PD-L1, and it might be expected that immunotherapy would not be effective in this population.

The toxicity profiles of these combinations must be further evaluated. FGFR tyrosine kinase inhibitors can

be associated with hyperphosphatemia, mucositis, and fingernail issues.

Another interesting combination is a CTLA-4 inhibitor plus a PD-1 inhibitor, such as ipilimumab (Yervoy, Bristol Myers Squibb) plus nivolumab (Opdivo, Bristol Myers Squibb). The CheckMate 032 trial in patients with previously treated metastatic urothelial carcinoma showed a response rate of 38% for ipilimumab plus nivolumab compared with approximately 25% for nivolumab. In the PD-L1–positive population, the response rate was 59% with ipilimumab plus nivolumab. These provocative results led to a large, randomized phase 3 trial comparing doublet immunotherapy vs platinum-based chemotherapy in the first-line setting (CheckMate 901), but results are not yet available.

Other research is evaluating multitargeted vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors, such as cabozantinib (Cabometyx, Exelixis), and an investigational agent called sitravatinib, in combination with immune checkpoint inhibitors. Combinations of a VEGFR2 inhibitor and an immune checkpoint inhibitor are being developed in multiple diseases, and already approved for endometrial cancer (eg, lenvatinib [Lenvima, Eisai] and pembrolizumab). The idea is that these therapies might modulate the tumor micro-environment in immunotherapy-resistant tumors and allow reinvigoration of the immune response in patients who developed progressive disease during prior treatment with checkpoint inhibitors. Cabozantinib is approved for indications such as medullary thyroid cancer (its first approval), hepatocellular cancer, and kidney cancer, but not bladder cancer. Cabozantinib was tested in urothelial carcinoma as a single agent in a recent phase 2 trial from the National Cancer Institute. The objective response rate was 19% among 42 evaluable patients. Further evaluation of cabozantinib in combination with immune checkpoint inhibition in bladder cancer is ongoing.

A phase 2 study presented at the 2020 ESMO virtual congress of sitravatinib in combination with nivolumab found a higher than expected response rate in patients with advanced or metastatic urothelial carcinoma previously treated with a platinum therapy but who were checkpoint inhibitor–naïve. This combination also has shown promise in patients with immune checkpoint inhibitor–refractory disease. These results suggest that the combination of a VEGF-receptor tyrosine kinase inhibitor plus a checkpoint inhibitor in bladder cancer, similar to kidney cancer, might be a useful strategy.

Disclosure

Dr Rosenberg is a consultant for Astellas, Seattle Genetics, Mirati, BMS, Merck, Genentech, AstraZeneca, Lilly, Boeh-

ringer Ingelheim, GlaxoSmithKline, Pfizer, EMD-Serono, Bayer, Janssen, Roche/Genentech, and QED. He has received clinical trial funding from Bayer, Astellas, Seattle Genetics, Roche/Genentech, and QED.

Suggested Readings

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