The Changing Treatment Landscape for Metastatic Urothelial Carcinoma

Presented by Thomas W. Flaig, MD

Abstract

Urothelial carcinoma is the predominant histologic type of bladder cancer. After 30 years of minimal progress in the treatment of advanced-stage disease, recent advances in the genomic characterization of urothelial cancer and breakthroughs in bladder cancer therapeutics have rejuvenated the field. Nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab are among the exciting recent novel therapeutic advances gaining approvals by the FDA for treatment of advanced-stage urothelial carcinoma. Yet the challenge for clinicians is to determine the optimal choice of agents as first-line or second-line therapy and which offers the best chance for overall survival for the individual patient in this rapidly changing field.

“After decades without new bladder cancer treatments, in the past 2 years, and even more so in the past 6 to 9 months, approvals and clinical integration of new drugs have accelerated. We’re finally getting traction against the disease,” according to Thomas W. Flaig, MD, Associate Dean for Clinical Research, University of Colorado School of Medicine; Chief Clinical Research Officer, UCH; and Chair of the NCCN Guidelines Panel for Bladder Cancer. At the NCCN 23rd Annual Conference, Dr. Flaig acknowledged this news and described the systemic treatment options for first- and second-line metastatic urothelial bladder carcinoma (Figure 1). In addition, Dr. Flaig compared the similarities and differences among new immunotherapy options for bladder cancer and reviewed key data supporting their use in patients with metastatic urothelial bladder carcinoma.

Standard treatment for patients with muscle-invasive, nonmetastatic bladder cancer includes cisplatin-based chemotherapy followed by surgical removal of the bladder or radiation therapy and concomitant chemotherapy. Immunotherapy is emerging as an important treatment for patients with metastatic disease who do not benefit from first-line chemotherapy, and has been added to the updated NCCN Guidelines for Bladder Cancer.

In his presentation on approaches to managing bladder cancer, Dr. Flaig noted that drugs that work in lung cancer also seem to be of benefit in bladder cancer, including platinum-based combinations, gemcitabine, taxanes, and immunotherapy. Dr. Flaig emphasized that “more than 17,000 deaths from bladder cancer are estimated to occur in 2018.” In addition, he noted, “75% of patients are male and many of the patients are or were smokers.”

Immune Checkpoint Inhibitors

Perhaps the most exciting aspect of the recent surge in treatments to manage bladder cancer is the use of immune checkpoint inhibitors (ICIs). “We really needed innovation in bladder cancer,” Dr. Flaig said. “Checkpoint inhibitors are a more targeted way to approach late-stage bladder cancer.”

Two checkpoint inhibitors (atezolizumab and pembrolizumab) have been used as first-line treatment in pa-
response rates were higher with pembrolizumab than with chemotherapy (21% vs 11%). Most of the responses were in the first 6 months. The most common adverse reactions reported for at least 20% of pembrolizumab-treated patients included fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea, diarrhea, constipation, and rash.\(^8\)

**Atezolizumab**

Dr. Flaig reviewed data from a randomized phase III study of atezolizumab (1,200 mg) every 3 weeks versus chemotherapy (vinflunine, paclitaxel, or docetaxel) in 931 patients with metastatic urothelial carcinoma who experienced disease progression after platinum-based chemotherapy.\(^9\) “Interestingly,” commented Dr. Flaig, “atezolizumab did not increase the OS in [patients with] PD-L1–overexpressing (immunohistochemistry 2/3) urothelial carcinoma.” However, the researchers concluded that atezolizumab showed a meaningful duration of response in a subset of patients.

**Immunotherapy Combinations**

Dr. Flaig delved into combining conventional cancer therapies (such as chemotherapy, radiation, or targeted therapy) and ICI therapies. “This approach may improve the response rate and benefit more patients with cancer because of tumor cell death caused by conventional therapies. The activated immune cells then travel to the damaged tumor tissue, and these immune cells’ functions could be further enhanced by ICIs.”

Of importance looking forward, Dr. Flaig noted, is the group of patients who are less likely to show response to ICIs. “They should be the next targets for clinical evaluation. However, the issue of patient selection is a priority based on the availability of so many similar compounds,” he said.

Overall, cancers with the highest mutational burden, such as bladder cancer, seem to benefit the most from immune checkpoint blockade because of the greater T-cell–mediated antitumor immune response elicited by these cancers.\(^10\)

**Other Considerations**

Although the respective clinical trials for all the agents in this class have shown that efficacy cor-
relates with PD-L1 expression, responses have also been seen in patients whose tumors tested negative for PD-L1. Although the presence of PD-L1 can be predictive of response, the lack of PD-L1 expression should not preclude the use of these agents at this point of biomarker development because some patients with negative test results have exhibited responses.

Combination therapies to overcome innate resistance by targeting putative mechanisms of immune evasion within the tumor microenvironment are in various stages of development. According to Dr. Flaig, “they are showing promise as a means of personalizing cancer immunotherapy and potentially enhancing immune memory.”

More recent novel immunotherapy drugs (eg, ALT-801 [a tumor-targeted interleukin-2] and ALT-803 [an interleukin-15 superagonist complex]) have been tested in bladder cancer, with promising antitumor activity. As we start to understand the genetic and nongenetic basis of immunotherapy responders,” emphasized Dr. Flaig, “we are seeing the potential predictors for such treatment, and these predictive biomarkers will be critical in the rational clinical advancement of these therapy.”

National Clinical Trials Network

The National Clinical Trials Network is an entity that should become familiar to both clinicians and patients. Through this network, newer advanced agents are being discovered for patients with metastatic bladder cancer. Because most patients with stage IV bladder cancer have disease that has already spread and cannot be removed with surgery, systemic treatment is necessary. Clinical trials are available for most stages of bladder cancer. Patients who are interested in participating in a clinical trial should discuss the risks and benefits of clinical trials with their physician.

References