The advent of targeted agents, such as enfortumab vedotin, erdafitinib, and sacituzumab govitecan, have revolutionized the treatment of metastatic urothelial cancer. Although these novel therapies have demonstrated favorable efficacy outcomes, their toxicity must be carefully monitored. The NCCN Guidelines for Bladder Cancer recommend platinum-based chemotherapy in this clinical context, but the combination of targeted and immunotherapeutic agents may have the potential to replace it as frontline standard of care.

"We are getting closer to [optimizing a] targeted, personalized therapy for our patients with bladder cancer," commented Arlene O. Siefker-Radtke, MD, Professor of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, and a member of the NCCN Bladder Cancer Guidelines Panel. At the NCCN 2023 Annual Conference, she discussed the safety and efficacy of emerging targeted therapies, which, when combined with immunotherapeutic agents, may outperform platinum-based chemotherapy and transform standard of care in this clinical context.

**Targeted Therapy**

**Enfortumab Vedotin**

"Following this frontline standard, we now have multiple targeted agents," commented Dr. Siefker-Radtke. She began by discussing enfortumab vedotin, which was the first antibody–drug conjugate to be approved for the treatment of metastatic urothelial carcinoma. Its target, Nectin-4, is expressed in 83% of patient samples; thus, testing for this transmembrane protein is not required prior to treatment. The phase III EV-301 trial demonstrated improved median overall survival (OS; 12.9 vs 9.0 months) and progression-free survival (PFS; 5.5 vs 3.7 months) outcomes with enfortumab vedotin versus investigator’s choice in patients who received a prior platinum-containing chemotherapy regimen and had experienced disease progression during or after PD-1/PD-L1 inhibition; the objective response rates (ORRs) were 40% and 18%, respectively. After a longer duration of follow-up, this Nectin-4–directed antibody–drug conjugate continued to show an OS benefit.

"This is certainly a treatment that is here to stay," Dr. Siefker-Radtke stated. "However, there is toxicity [with enfortumab vedotin]." Rash, peripheral neuropathy, vision problems, and hyperglycemia were among the most frequently reported adverse events with enfortumab vedotin in this trial. Of note, the prescribing information carries a black box warning for Stevens-Johnson syndrome.

Compared with the aforementioned data, primary findings from cohort 2 of the multicenter phase II EV-201 trial revealed similar OS (14.7 months) and PFS (5.8 months) outcomes in patients with cisplatin-ineligible
bladder cancer compared with enfortumab vedotin. However, this population was found to experience more treatment-related adverse events (55%), including deaths (n=4), than patients with cisplatin-eligible disease. “I think [the reason we see more toxicity in this population] deals with how we are clearing enfortumab vedotin; the majority of this compound is cleared in the liver,” Dr. Siefker-Radtke commented. “We should use caution when using this in platinum-ineligible patients, [especially in] those with cirrhotic livers.”

**Erdafitinib**

Erdafitinib was the first biomarker-directed therapy to be approved for metastatic urothelial carcinoma. The efficacy and safety of this FGFR inhibitor were evaluated in the phase II BLC2001 trial of patients with FGFR-altered disease; based on the results of an interim analysis, the starting dose was established as 8 mg per day, with potential uptitration to 9 mg per day, in a continuous regimen. The ORR was 40%, and 77% of the study population experienced a reduction in the sum of target-lesion diameters. With a longer duration of follow-up, treatment with the selected regimen of erdafitinib continued to demonstrate antitumor activity. Median rates of PFS and OS were 5.5 and 11.3 months, respectively.

“We do not yet have a truly nontoxic therapy,” Dr. Siefker-Radtke commented. She noted that hyperphosphatemia, nail changes (onycholysis and paronychia), palmar–plantar erythrodysesthesia, and central serous retinopathy were frequently reported in this population. Clinicians should be informed about how to prevent and treat these conditions, which may include dose modifications, over-the-counter and prescription medications, lifestyle adjustments, and, when necessary, referral to a specialist for further evaluation and management.

“Keep in mind [that] most people do need to hold erdafitinib after approximately 2.0 to 2.5 months of treatment, but are then able to resume therapy” Dr. Siefker-Radtke stated.

**Sacituzumab Govitecan**

The highly specific antibody–drug conjugate sacituzumab govitecan is designed to target Trop-2; this transmembrane glycoprotein has been found to be expressed in approximately 83% of metastatic urothelial cancers, rendering testing unnecessary before treatment. Sacituzumab govitecan employs a hydrolysable linker to facilitate targeted delivery in malignant cells.

“[This] probably accounts for more of the toxicity,” commented Dr. Siefker-Radtke. “There is more hydrolysis in the circulation, resulting in systemic absorption and systemic release.”

Based on the primary results from cohort 1 of the phase II TROPHY-U-01 trial, sacituzumab govitecan demonstrated an ORR of 27% in patients who experienced disease progression after undergoing platinum-based combination chemotherapy and checkpoint inhibition. The median durations of PFS and OS were 5.4 and 10.9 months, respectively. “Some of these patients had been heavily pretreated, including [with] prior enfortumab vedotin,” Dr. Siefker-Radtke remarked. “I think we need more data to see where the ORR settles out in comparison to some of the other targeted strategies.”

Despite the aforementioned positive outcomes, it is important to note that patients treated with sacituzumab govitecan may experience side effects. Neutopenia, including febrile neutropenia, and diarrhea, nausea, and vomiting were among the most frequently reported treatment-related adverse events in the study population. “Patients with bladder cancer, in general, are [older and] may have had prior chemotherapy regimens, so there could be reasons why their bone marrow is a bit more fragile in the treatment setting compared with a patient population with breast cancer,” commented Dr. Siefker-Radtke. “I personally am using growth factor support in all of my patients in [the setting of] sacituzumab govitecan because of neutropenia and neutropenic fever.”

**Combining Targeted Therapy With Immunotherapy**

“We are seeing a lot of excitement for [targeted therapy and immunotherapy] combinations,” Dr. Siefker-Radtke remarked. In patients with treatment-naive, cisplatin-ineligible disease, enfortumab vedotin + pembrolizumab has demonstrated an ORR of approximately 73%. [Editor’s Note: Combination enfortumab vedotin + pembrolizumab was granted FDA accelerated approval on April 2, 2023, for use in frontline treatment metastatic, surgically unresectable cisplatin-ineligible bladder cancer.]”

“There is a lot of hope that this combination may change the frontline standard for cisplatin-ineligible patients with bladder cancer,” she commented. “I hope that maybe we now have a strategy that can beat platinum in general and result in less toxic therapy for our patients.”

However, despite the aforementioned clinical benefits, patients treated with enfortumab vedotin + pembrolizumab may still experience toxicities. Neuropathy, fatigue, and alopecia, as well as enfortumab vedotin–associated side effects, such as Stevens-Johnson syndrome, peeling of the skin, diabetic ketoacidosis, and diarrhea, have been reported.
Combination erdafitinib + cetrelimab has also demonstrated antitumor activity in metastatic urothelial cancer. Early results of the phase II NORSE trial have revealed ORRs of 68% and 33% with and without the addition of cetrelimab, respectively, in treatment-naïve, cisplatin-ineligible patients with FGFR-altered tumors. “This combination is based on the idea that the FGFR-altered tumors tend to be ‘immunologically cold,’” Dr. Siefker-Radtke remarked. “They don’t have a lot of immune cells and, if you profile their genes, the immune response genes seem to be dysregulated or ‘turned off’ in these tumors.”

Of note, compared with the aforementioned combinations, data from cohort 3 the TROPHY-U-01 trial revealed a lower ORR with sacituzumab govitecan + pembrolizumab (34%). “It is possible that sacituzumab govitecan, being more myelosuppressive, induces more lymphopenia,” Dr. Siefker-Radtke explained. “Perhaps eradication of lymphocytes is resulting in the lack of additive to synergistic benefit.”

Disclosures: Dr. Siefker-Radtke has disclosed receiving grant/research support from Bristol-Myers Squibb, Janssen Pharmaceutica Products, LP, Merck & Co., Inc., Millennium Pharmaceuticals, Inc., and Nektar Therapeutics, receiving consulting fees from Gilead, Janssen Pharmaceutica Products, LP, Loxo Oncology, Merck & Co., Inc., Seattle Genetics, and Taiho Pharmaceuticals Co., Ltd.; and receiving honoraria from Janssen Pharmaceutica Products, LP.

Correspondence: Arlene O. Siefker-Radtke, MD, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Email: asiefker@mdanderson.org

References