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HER2 in Bladder Cancer: Breaking Through the Molecular Frontier

Urothelial carcinoma (UC) represents the most common histologic subtype of bladder cancer and continues to be a clinically challenging malignancy, particularly in the advanced setting.[1] Despite progress in systemic therapies made over the past decade, the prognosis for patients with advanced disease remains poor.[1,2] Human epidermal growth factor receptor 2 (HER2) has recently emerged as a relevant biomarker in advanced UC (aUC), with growing recognition of its potential as a therapeutic target.[2] Increasing evidence from recent studies indicates that HER2 expression is relatively prevalent in this disease, prompting interest in therapeutic strategies that specifically target HER2. Among these, novel HER2-directed antibody-drug conjugates (ADCs) have demonstrated encouraging efficacy in clinical trials. [1,2] One of the HER2-directed ADCs, trastuzumab deruxtecan, has received accelerated approval from the FDA for a tumor-agnostic indication for patients with unresectable or metastatic HER2-positive solid tumors who have previously received systemic therapy and lack other treatment options.[3] These advances underscore the essential role of routine HER2 testing to optimize therapy selection, thereby improving outcomes and effectively integrating HER2-directed therapies into contemporary clinical practice.

HER2 as a Molecular Target in Urothelial Cancer

A recent study of a large, commercially sourced, global cohort of more than 2,000 tumor samples from patients with aUC highlighted the prevalence of HER2 expression when assessed using immunohistochemistry (IHC) and dual in situ hybridization (DISH) in this patient population.[4] Specifically, high-level HER2 expression, defined as IHC 3+, was identified in approximately 13% of all patients tested, while over 50% of tumors exhibited some degree of HER2 protein expression (IHC 1+, 2+, or 3+).[4] These findings support the growing recognition of HER2 as a meaningful biomarker in aUC and reinforce the importance of incorporating routine HER2 testing into standard clinical workflows.

Importance of HER2 Testing and Guidelines Recommendations

HER2 testing using IHC is now formally recommended by clinical guidelines for all patients diagnosed with aUC.[5] Early testing, performed close to the time of diagnosis of advanced disease, can facilitate timely and effective therapeutic decisions, especially if patients progress to metastatic disease. Conducting HER2 testing at this earlier stage, particularly when tissue from cystectomy is available, allows clinicians to have a clearer understanding of the underlying molecular profile of the tumor when systemic therapy is being considered. Knowledge of a patient's HER2 expression status is essential for optimal patient selection, particularly as HER2-targeting ADCs gain regulatory approval and become increasingly available for clinical use.

"HER2 testing via immunohistochemistry is the new practice standard in advanced urothelial cancer. All patients with advanced and metastatic disease should be tested."

- Vadim S. Koshkin, MD

Trastuzumab Deruxtecan: Clinical Evidence and Trial Insights

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Trastuzumab deruxtecan is a HER2-targeted ADC consisting of the HER2 monoclonal antibody trastuzumab linked to a topoisomerase I inhibitor chemotherapy payload. This agent has received pan-tumor FDA approval for patients with HER2 IHC 3+ advanced solid tumors, a group that includes patients with aUC.[3] The approval of trastuzumab deruxtecan was primarily based on results from the DESTINY-PanTumor02 trial, a multi-cohort, phase 2 study that enrolled patients with HER2-expressing advanced solid tumors, including 41 patients with bladder cancer, who received trastuzumab deruxtecan 5.4 mg/kg once every 3 weeks.[6] All enrolled patients had tumors with HER2 expression at the IHC 2+ or 3+ level and had received at least one prior systemic therapy. Among the 267 patients across all tumors who received at least one dose of trastuzumab deruxtecan, the primary endpoint of objective response rate (ORR) was 37.1% with a median duration of response (DoR) of 11.3 months. In 75 patients across all tumors who had HER2 IHC 3+ expression, ORR was 61.3% and the median DoR was 22.1 months. Responses were seen in all tumor types, including gynecologic cancers, biliary tract cancers, and bladder cancer. Within the bladder cancer cohort, the ORR was 39% with a median DoR of 8.7 months. Notably, in the subgroup of patients whose tumors exhibited IHC 3+ HER2 expression, ORR was 56.3%. In this same subgroup of HER2 IHC 3+ patients, the median progression-free survival (PFS) was 7.4 months, and the median overall survival (OS) was 13.4 months. Grade ≥3 drug-related adverse events were observed in 40.8% of patients with the most common being neutropenia and anemia. Adjudicated drug-related events of interstitial lung disease (ILD)/pneumonitis occurred in 10.5% of patients, with the majority being low-grade events. These results showed the clinical activity of trastuzumab deruxtecan in patients with HER2-positive solid tumors and directly supported its regulatory approval for use in patients with IHC 3+ HER2 expression. In the current NCCN Guidelines for bladder cancer, trastuzumab deruxtecan is listed as a preferred second-line regimen for biomarker-selected patients (HER2 IHC 3+) with advanced disease after first-line enfortumab vedotin plus pembrolizumab.[5]

Disitamab Vedotin: Emerging Data and Future Directions

Disitamab vedotin is an investigational HER2-targeted ADC currently in phase 3 clinical development for aUC. It is composed of a HER2-directed monoclonal antibody conjugated to the cytotoxic agent monomethyl auristatin E (MMAE).[7]

In a combined analysis of two phase 2 trials conducted in China, disitamab vedotin demonstrated response rates around 50% in patients with progressive aUC whose tumors expressed HER2 at IHC 2+ or 3+.[7] In a separate phase 2 trial, nearly 40% of patients with pretreated aUC and lower HER2 expression (IHC 1+) responded to disitamab vedotin, suggesting that HER2-targeted therapies may be effective in a wider range of expression levels than previously considered.[8]

Importantly, combination approaches using disitamab vedotin with immune checkpoint inhibitors have also shown encouraging efficacy in previously untreated HER2-expressing aUC. Early results from a small cohort of 20 patients with HER2-expressing aUC treated with first-line disitamab vedotin and pembrolizumab showed an impressive ORR of 75%, offering preliminary evidence of efficacy.[9] A recent press release on results from a phase 3 trial conducted in China of first-line disitamab vedotin plus toripalimab vs platinum-based chemotherapy in patients with HER2-expressing aUC (IHC 1+, 2+, or 3+) announced that the study has met its dual primary endpoints of PFS and OS, with full data to be presented at an upcoming meeting.[10]

Additionally, an ongoing global phase 3 trial is currently evaluating first-line disitamab vedotin in combination with pembrolizumab vs platinum-based chemotherapy in patients with any degree of HER2-expressing aUC (IHC 1+, 2+, or 3+).[11]

Multidisciplinary Management of Toxicities Associated With HER2-Directed ADCs

It is essential that clinicians become familiar with HER2-directed ADCs, including their toxicity profiles and adverse event management. As these therapies become more widely used, understanding their risks and benefits will be crucial to optimizing patient outcomes. Each ADC has a distinct toxicity profile that requires careful and proactive monitoring and effective management.[12] For trastuzumab deruxtecan, the most commonly reported adverse events were related to its topoisomerase I inhibitor payload and included fatigue, nausea, alopecia, diarrhea, and various cytopenias.[6] A rare but potentially serious adverse event associated with trastuzumab deruxtecan is ILD/pneumonitis, which occurred in roughly 10% of patients in the DESTINY-PanTumor02 trial. While often asymptomatic and detected only through imaging, it can become clinically significant if not addressed early. Prompt drug interruption, close monitoring, and evaluation by a pulmonologist are recommended in cases where ILD/pneumonitis is suspected.[13]

Disitamab vedotin, due to its MMAE payload, presents a different toxicity profile. A combined analysis of two phase 2 clinical trials reported that the most common treatment-related adverse events were peripheral sensory neuropathy, leukopenia, neutropenia, increase in AST and ALT, alopecia, asthenia, and decreased appetite.[7] Although comprehensive global safety data are still being collected, these adverse events were generally consistent with other MMAE-containing ADCs.

Optimal management of ADC-related toxicities requires a collaborative, team-based approach involving medical oncologists, nurses,

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nurse practitioners, and specialists such as pulmonologists and neurologists when necessary.[14] Collaboration across specialties allows for proactive monitoring, early complication recognition, and coordinated care delivery, ensuring patients receive the full benefit of treatment while minimizing risks.[15]

"In terms of managing the treatment with trastuzumab deruxtecan and potential adverse events, it really takes a village and requires a multidisciplinary team aside from medical oncologists including nurse practitioners and nurses as well as potential involvement of other specialists based on certain toxicities."

- Vadim S. Koshkin, MD

Key Takeaways

Patient selection is a critical component in the effective use of HER2-targeted ADCs in aUC. Accurate and timely identification of HER2 expression status is critical for optimizing therapeutic alignment and ensuring that molecularly targeted agents are appropriately matched to the patients most likely to derive clinical benefit.[2] Currently, trastuzumab deruxtecan is approved for patients with IHC 3+ HER2 expression, and based on existing data, approximately 10%–15% of patients with aUC are likely to qualify for this treatment.[1] As ongoing clinical trials continue to evaluate HER2-targeted ADCs in broader patient populations, including those with lower levels of HER2 expression, the number of patients eligible for these therapies will potentially increase. This underscores the importance of routine HER2 testing and early identification of HER2-positive tumors to make the best use of HER2-targeted ADCs, which offer a robust, innovative, and rapidly evolving therapeutic option for an expanding population of patients with advanced bladder cancer.

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