Immune Checkpoint Inhibitors for Urothelial Cancer: An Update on New Therapies

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Ongoing trials are evaluating immune checkpoint inhibitors—used alone, in combination with cytotoxic, targeted, radiation therapies, or with other such inhibitors—for therapy in patients with advanced bladder cancer.

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An essential feature of cancer is its ability to evade the immune system. Multiple mechanisms are used for this purpose, including the disruption of antigen presentation and suppression of the immune response. The latter mechanism involves the activation of T-cell inhibition by recruiting regulatory T cells that weaken this response. Recent progress in understanding the ability of cancer to evade the immune system has paved the way to develop strategies to reverse this process and reactivate the immune system. Particularly, immune checkpoint signaling between T cells and tumor cells has been targeted with a new class of drug, immune checkpoint inhibitors. Immunotherapy has been an established and effective treatment in bladder cancer since 1976 when Morales and colleagues demonstrated that intravesical treatments with bacillus Calmette-Guérin can treat carcinoma in situ and prevent nonmuscle invasive urothelial cancer recurrence.[1,2] This treatment elicits a cytotoxic response via antigenic presentation by bladder tumor cells.

Cytotoxic T-lymphocyte-associated protein (CTLA)-4, programmed death-1 (PD-1) and programmed death-ligand-1 (PD-L1) are molecules that downregulate the immune response and are targets of therapeutic antibodies that have demonstrated clinical efficacy across a wide range of malignancies. Five such agents—pembrolizumab, atezolizumab, nivolumab, avelumab and durvalumab—were recently approved by the US Food and Drug Administration (FDA) for clinical use in patients with advanced urothelial cancers.[3] This class of agents also has been approved for several other malignancies, most notably in melanoma, non-small cell lung cancer, and renal cell carcinoma.[3]

IMMUNE BIOLOGY

CTLA-4 is expressed on activated CD4 and CD8 T cells and competes with CD28 on T cells to interact with the costimulatory B7 proteins on antigen presenting cells. The CD28/B7 interaction promotes T-cell activation and effector functions, and the CTLA-4/B7 interaction inhibits them. In addition, PD-1 is a receptor expressed on CD4 and CD8 T cells, T regulatory (Treg) cells, B cells and natural killer (NK) cells that interacts with its ligand PD-L1 to suppress the immune response. Urothelial cancer possesses features that make it an adequate target for immunotherapeutic agents. Primarily, it is characterized by a high-mutation load, which lends itself to an increased expression of immunogenic antigens on tumor cells.[4]

Immunotherapy Treatments in Cisplatin-Ineligible Patients

Cisplatin-based chemotherapy is the first-line treatment and standard of care in unresectable or metastatic urothelial cancer. However, many patients are unable to receive cisplatin secondary to renal dysfunction, poor performance status, or other comorbidities. Alternative cytotoxic therapies in the first-line setting such as carboplatin-based regimens are associated with inferior outcomes and poor tolerability. There is, therefore, a need for effective and well-tolerated therapies in cisplatin-ineligible patients (Table).

In the phase 2 Keynote-052 trial, 370 cisplatin-ineligible patients were treated with the anti-PD-1 antibody pembrolizumab 200 mg every 3 weeks for up to 2 years.[5] At a median follow-up of 9.5 months, the objective response rate (+ORR) was 29% for the entire cohort, with a 7% complete response (CR) rate, and a 22%

partial response (PR) rate.[5] The median duration of response had not been reached at the time of analysis. Responses were seen regardless of PD-L1 expression, although high response rates were noted in patients whose tumors had PD-L1 expression > 10%. Pembrolizumab had an acceptable tolerability profile in this population. The most common grade 3 or 4 treatment-related adverse event (AE) was fatigue at 2%; 5% of patients discontinued therapy due to treatment related AEs, whereas 17% of patients had immune-mediated AEs.[5]

Similarly, in a single-arm phase 2 trial, atezolizumab, an anti-PD-L1 antibody, dosed at 1,200 mg every 3 weeks was used as first-line therapy in 119 patients with advanced urothelial cancer who were cisplatin ineligible. At a median follow-up of 17 months, the ORR was 23%, with a 9% CR rate. The median duration of response had not been reached. Median progression free survival (PFS) was 2.7 months, whereas overall survival (OS) was 16 months. Eight percent of patients had an AE leading to treatment discontinuation, and 17% had immune-mediated AEs.[6] Both pembrolizumab and atezolizumab were granted FDA approval in 2017 for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-based chemotherapy.[3]

TABLE

Immunotherapy Clinical Trials in Advanced Urothelial Cancer

Study	Setting	Phase	Agent(s)	Patients No.	ORR, %	PFS, mo	OS, mo
Keynote 052[5]	1st line	2	Pembrolizumab	370	24	2.0	N/A
IMvigor 210[6]	1st line	2	Atezolizumab	119	23	2.7	15.9
Keynote 045[7]	2nd line	3	Pembrolizumab Chemotherapy	542	21.1 11.4	2.1 3.3	10.3 7.4
Checkmate 275[8]	2nd line	2	Nivolumab	270	19.6	2.0	7.0
IMvigor 211[9]	2nd line	3	Atezolizumab Chemotherapy	931	13.4 13.4	2.1 4.0	11.1 10.6
JAVELIN[10]	2nd line	1	Avelumab	249	17.0	6.6	6.5
NCT01693562[11]	2nd line	1 & 2	Durvalumab	191	17.8	1.5	8.2

Abbreviations: FDA, US Food and Drug Administration; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Immunotherapy Treatments After Progression With Cisplatin

Cytotoxic chemotherapy in the second-line setting with disease progression following platinum-based treatment has shown dismal responses, with a median OS of about 6 to 7 months.[7] Immunotherapy provides an effective and a much-needed option in this scenario.

Five antibodies targeting the PD-1/PD-L1 pathway, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, have been granted FDA approval for patients who have progressed during or after platinum-based therapy (Table).[3] In the phase 3 Keynote-045 trial, 542 patients were randomly assigned to receive either pembrolizumab 200 mg administered every 3 weeks or investigator's choice chemotherapy (paclitaxel, docetaxel, or vinflunine).[7] Median OS was 10.3 months in the pembrolizumab group and 7.4 months in the chemotherapy group (hazard ratio for death, 0.73; $P = .002$). Serious (grade 3 or above) treatment-related AEs were significantly less frequent with pembrolizumab (15% vs 49.4%).[7] In a phase 2 trial, 270 patients were treated with nivolumab, a PD-1 inhibitor, at a dose of 3 mg/kg given every 2 weeks.[8] The ORR was 19.6%, while the median OS for the entire cohort was 7 months. Responses were seen at all levels of PD-L1 expression, although in patients whose tumor expressed PD-L1 ≥1%, median OS was 11.3 months.[8]

It should be noted that in a large phase 3 trial comparing atezolizumab with chemotherapy in the second-line setting, ORR and OS were not statistically different between the 2 groups, although the duration of response was longer with atezolizumab.[9] In early phase trials, avelumab and durvalumab, both PD-L1 inhibitors showed an ORR of about 17%, with higher ORR seen in patients with tumors positive for PD-L1 expression.[10,11] The AE profile of immune checkpoint inhibitors is relatively favorable in clinical trials. The American Society of Clinical Oncology and National Comprehensive Cancer Network have jointly published evidence-based guidelines for the management of their immune related AEs.[12]

FUTURE DIRECTIONS

Several challenges have emerged with immunotherapy treatments. One issue is the relatively low ORRs for immune checkpoint inhibitors, ranging from 13.4% to 24% depending on the trial. Therefore, there is a need to

identify reliable biomarkers and selection criteria to predict their efficacy and improve patient selection. Although tumor PD-L1 expression has shown some usefulness in this setting, responses have been noted in patients whose tumors have low or no expression of PD-L1. This low predictive accuracy is caused by several factors, including PD-L1 intratumor expression heterogeneity, primary vs metastatic site PD-L1 expression heterogeneity, lack of consensus on which PD-L1 assays and which value cutoffs to use, and the differences seen in marker expression depending on the freshness of the tissue specimen.

Other predictive biomarkers with potential include tumor gene expression profiles/tumor mutational load, T-cell and B-cell signatures. The optimal imaging modality and timing of this imaging for response assessment also is uncertain. So-called tumor pseudo-progression seen on imaging after treatment with these agents as a result of the immune/inflammatory response to the tumor is now a well-recognized phenomenon, but it can be challenging to differentiate from true disease progression. Other challenges include deciding on which immune checkpoint inhibitor to use given a lack of head-to-head comparisons of these immunotherapeutic agents, finding the proper drug doses to maximize efficacy, as well as determining the optimal duration of treatment in patients with continued response to immunotherapy. Many oncologists continue these treatments for up to 2 years in the setting of a significant or complete response.

CONCLUSION

Immune checkpoint inhibitors have emerged as pivotal treatments for patients with advanced urothelial cancer who are unfit to receive cisplatin in the first-line setting or who experience disease progression after cisplatin-based chemotherapy. This field continues to expand at a rapid pace due to multiple ongoing clinical trials assessing these agents, whether alone, in combination with cytotoxic, targeted, radiation therapies, or with other immune checkpoint inhibitors, both in the advanced as well as the neoadjuvant/adjuvant settings.

AUTHOR DISCLOSURES

The authors report no actual or potential conflicts of interest with regard to this article.

DISCLAIMER

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