Immunotherapy with Checkpoint Blockade in the Treatment of Urothelial Carcinoma

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Purpose: Although immunotherapy has a long history in the treatment of urothelial carcinoma, its use was limited to intravesical therapy for nonmuscle invasive disease. The development of immune checkpoint blockers for systemic delivery has expanded the application of immunotherapy to advanced metastatic urothelial cancers.

Materials and Methods: The PubMed® database was searched for publications regarding immune checkpoint blockers for the treatment of patients with urothelial carcinoma. Relevant congress abstracts were identified through searches of individual congress websites.

Results: A summary of the biology and immunology of urothelial carcinoma provides context to aid in discussing key data pertaining to immune checkpoint blockers that are approved and in development. We address immune mediated adverse events that are unique to immunotherapies and review diagnostic tools that may be useful to identify patients who would most benefit from immunotherapy.

Conclusions: Immunotherapies for urothelial carcinoma have shown clinical efficacy in select patients as well as a manageable safety profile. Studies are ongoing with the aim of expanding the proof of efficacy in metastatic disease and providing additional treatment options for patients with earlier stages of urothelial carcinoma.

Key Words: urinary bladder neoplasms, carcinoma, programmed cell death 1 receptor, immunotherapy

Abbreviations and Acronyms

APC = antigen-presenting cell
BCG = bacillus Calmette-Guérin
CD = cluster of differentiation
CR = complete response
CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4
DOR = duration of response
FDA = United States Food and Drug Administration
FGFR3 = fibroblast growth factor receptor 3
ICB = immune checkpoint blocker
IFN = interferon
imAE = immune mediated adverse event
MIBC = muscle invasive bladder cancer
mUC = metastatic urothelial carcinoma
NMIBC = nonMIBC
ORR = overall response rate
OS = overall survival
PD-1 = programmed cell death-1
PD-L1 = programmed cell death ligand-1
TCGA = The Cancer Genome Atlas
TRAE = treatment related adverse event
TURBT = transurethral bladder tumor resection
UC = urothelial carcinoma

Urothelial carcinoma of the bladder, the sixth most common cancer in the United States, can be categorized into 3 main disease states based on clinical staging, including NMIBC, MIBC and mUC. At diagnosis about 70% of patients with UC present with NMIBC, which includes Ta, T1 and

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carcinoma in situ. These patients are treated with localized therapies, including TURBT and in some patients adjuvant intravesical chemotherapy or BCG therapy. Other intravesical therapies, including IFNα, in combination with BCG and single agent chemotherapies have not demonstrated superiority to monotherapy with BCG.

High grade NMIBC has a high rate of recurrence and can progress to MIBC. Approximately 30% of patients are initially diagnosed with MIBC (T2-T4, N0), which is typically treated with neoadjuvant cisplatin based chemotherapy followed by radical cystectomy or in select patients trimodal therapy (TURBT and chemoradiation). Despite aggressive therapy MIBC has an approximately 50% chance of progressing to incurable metastatic disease. Distant mUC, which is found in 5% of patients at diagnosis, is treated primarily with chemotherapy with a short response duration. Patients with metastases confined to the pelvic lymph nodes may be considered for surgical consolidation after chemotherapy with the possibility to achieve long-term survival.[1]

Although cytotoxic chemotherapy has long been the standard treatment of UC, ICB is a relatively new option. The first FDA approval of atezolizumab was in 2016, followed by nivolumab, durvalumab, avelumab and pembrolizumab for the treatment of locally advanced and mUC in the post-platinum setting.[2–6] In 2017 atezolizumab and pembrolizumab received FDA approval for cisplatin ineligible patients in the first line setting.[3,4]

We reviewed the role of the immune system in UC with a focus on ICBs for each disease state from NMIBC to mUC. The imAEs associated with ICBs are briefly reviewed and the general principles of imAE management are summarized. Finally, an overview of diagnostic testing in UC is provided, including available and investigational biomarker testing.

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UC develops along 2 molecular pathways.[7] The noninvasive papillary pathway is characterized by low grade, exophytic, noninvasive tumors that frequently demonstrate *RAS* and *FGFR3* alterations.[7] A small fraction of these tumors will undergo additional transformation to high grade disease, possibly accounting for the low frequency of *FGFR3* mutations seen in MIBC. The nonpapillary pathway, which is associated with inactivation of *RB1* and *TP53* genes, results in high grade NMIBC and MIBC.[7] This dual pathway concept has been enriched more recently by the description of molecular subtypes of UC based on RNA expression patterns (fig. 1). Different mRNA subtyping systems have been described by several investigators but they all share a basic division into basal and luminal subtypes, as is familiar from breast cancer, with additional specific subdivisions depending on the scheme.[8–11] *FGFR3* mutations previously observed in the papillary pathway appear enriched in the luminal subtype.[10] Basal tumors are enriched for markers of rapid proliferation and other stem cell associated markers, including elevated p63. Molecular subtyping continues to evolve as reflected by the recent presentation of an updated classification by TCGA based on analysis of its complete patient cohort.[12]

These molecular subtypes also appear prognostic. Several groups found that the basal subtype was associated with poor survival in MIBC.[10,11] These signatures may also have a role in predicting which patients benefit from chemotherapy[13,14] and immunotherapy,[15,16] although prospective studies are needed to verify these findings. In luminal tumors TCGA cluster I tumors have low expression of immune markers, including CTLA-4 and PD-L1, and cluster II tumors are immune infiltrated. Basal tumors (clusters III and IV) are also highly immune infiltrated but cluster IV tumors (claudin low) appear to be actively immune suppressed.

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Recent advances have improved our understanding of the role of the immune system in cancer. Under normal circumstances the immune system mounts a T-cell mediated antitumor response when tumor associated antigens are recognized as foreign, thereby leading to the destruction of tumor cells. In this way T cells are critical mediators of tumor immunity (fig. 2). However, tumor cells can continue to proliferate if they successfully evade recognition by the immune system.

Tumor cells maintain an immunosuppressive environment via multiple mechanisms, including the activation of inhibitory immune checkpoint molecules present on the surface of tumor and immune cells. ICBs are monoclonal antibodies that act to resensitize suppressed or immunoquiescent immune cells, thus, promoting an antitumor immune response. The T cell is activated via interaction with receptors on the surface of APCs.[17] Activated T cells express the receptor CTLA-4, which acts as a checkpoint to prevent excessive T-cell proliferation, ultimately inhibiting the interaction between the T cells and APCs.[17] In this way CTLA-4 has an essential role in maintaining the balance between immune activation and inhibition.[17] Ipilimumab and tremelimumab are monoclonal antibodies that bind to and block the activity of CTLA-4, thereby releasing the brake on T-cell proliferation and leading to enhanced T-cell activation.