Immunotherapy: The Wave of the Future in Bladder Cancer?

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Abstract

Urothelial cell carcinoma (UC) is one of the most common cancers and one of the most deadly. Metastatic UC is particularly hard to treat, because it is typically diagnosed when patients are elderly and have medical comorbidities. Many patients with metastatic UC are unable to receive cisplatin-based chemotherapy, due to older age at diagnosis and comorbidities, and even when platinum chemotherapy can be administered, it has limited success in prolonging survival. Recently, improved understanding of molecular targets and immunologic characteristics of urothelial tumor cells has resulted in new therapeutic approaches that may help optimize first- and second-line therapy. The most exciting of these approaches is inhibition of cytotoxic T-lymphocyte–associated antigen 4 or programmed cell death protein 1. These so-called "immune checkpoint" proteins are negative regulators of T-cell immune function, and inhibiting these proteins results in increased activation of the immune response to tumors. Two checkpoint inhibitors, atezolizumab and nivolumab, are now approved by the Food and Drug Administration as second-line therapy for advanced UC, and a wealth of clinical trials of these and other agents are ongoing. This review shows how oncology clinicians can incorporate checkpoint inhibitors into the management of patients with locally advanced or metastatic UC. It also introduces other forms of immunotherapy that are being investigated in bladder cancer: antibody-drug conjugates, vaccines, adoptive immunotherapy, and recombinant Bacillus Calmette–Guérin.

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Introduction

Bladder cancer is the sixth most common form of cancer in the United States and ranks fourth among men.[1] In 2017, it is expected that there will be 79,030 new cases of bladder cancer and 16,870 deaths due to the disease.[1] There is a male:female ratio of about 3:1 for new cases and about 2:1 for deaths.[1] Multiple factors may account for this, including the greater likelihood of men being smokers and their greater risk of occupational exposure to chemicals. Approximately 2.4% of men and women in the United States will be diagnosed with bladder cancer at some point during their lifetime, and an estimated 587,426 people are living with the disease.[2]

Worldwide, 90% of cancers that form in the bladder, the renal pelvises (the lower part of the kidneys), the ureters, and the proximal urethra derive from urothelium, a specialized mucous membrane.[3] The cancers are, therefore, called urothelial cell carcinoma (UC). Because the urothelium is also termed the transitional epithelium, UC is sometimes referred to as transitional cell carcinoma.

Urothelial carcinoma is divided into 3 categories, each differing in prognosis and management. Most new cases (70%-80%) are diagnosed as non–muscle-invasive UC (NMIUC), which is associated with a 15-year survival rate of 62% to 95%.[4] For these tumors, transurethral resection of bladder tumor is the standard of care, with adjuvant intravesical bacillus Calmette–Guérin (BCG) or intravesical chemotherapy added when the NMIUC is high-risk.

Twenty to 30% of cases are diagnosed at a later stage, when one or more tumors have invaded the muscularis mucosa, which forms a layer on the bladder wall.[4] This muscle-invasive disease (MIUC) can progress rapidly to metastatic disease, so it is treated much more aggressively, with partial or radical cystectomy, and with neoadjuvant or adjuvant chemotherapy.

The third category of disease, metastatic UC (mUC), is very challenging to treat, partly because bladder cancer is most frequently diagnosed between the ages of 75 to 84 years (median age at diagnosis 73 years), with only 2% of patients diagnosed before age 45.[2] Up to half of patients with mUC are unable to receive cisplatin-based chemotherapy, the standard of care for first-line treatment, due to poor performance status or medical comorbidities such as renal

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impairment, ischemic heart disease, or peripheral neuropathy.[5] For previously untreated patients who receive platinum chemotherapy, overall survival (OS) is about 9 to 15 months,[6] and the response rates with second-line chemotherapies are generally 20% or less, with median survival of 6 to 9 months.[7] Altogether, the 5-year survival rate for mUC is dismal, 5%.[2]

Thus, more effective and less toxic options for systemic treatment of advanced bladder cancer are urgently needed. As in certain other solid tumors, immune checkpoint inhibition is an exciting development in UC therapy. Atezolizumab and nivolumab are approved by the Food and Drug Administration (FDA) for second-line therapy, and a number of other checkpoint inhibitors are in clinical trials. This supplement reviews how oncology clinicians can incorporate checkpoint inhibitors into the management of patients with locally advanced or metastatic UC, and it introduces other forms of immunotherapy that are being investigated in bladder cancer.

The First Immunotherapy: BCG

Bacillus Calmette–Guérin, a weakened form of the bovine tuberculosis bacterium *Mycobacterium bovis,* was initially developed as a tuberculosis vaccine. In 1976, a Canadian oncologist, Alvaro Morales, described tumor responses in 4 of 10 patients who received intravesical BCG for NMIUC.[8] Subsequent randomized trials confirmed reduced rates of recurrence and progression, with positive effects on mortality. In 1990, the FDA approved intravesical BCG as the first cancer immunotherapy, and it has since become the gold standard for treating high-risk NMIUC. Multiple BCG substrains are used globally for UC immunotherapy, and they have different product characteristics and strengths, which lead to different dosing levels and schedules. However, all strains are effective and are considered clearly superior to intravesical chemotherapy.[9,10] The American Urological Association recommends 3 years of maintenance therapy for patients who can tolerate it.[11] The optimal schedule is unknown, but a schedule evaluated by the Southwestern Oncology Group in a randomized trial was associated with significantly increased recurrence-free survival compared with induction BCG alone.[12] In that study, BCG was instilled weekly for 3 weeks at months 3, 6, 12, 18, 24, 30, and 36 from the start of 6 weeks of induction therapy.

The most frequent adverse events (AEs) associated with BCG are urinary frequency, irritative bladder symptoms, hematuria, low-grade fever, and flu-like symptoms. These are generally tolerable with supportive care. However, severe AEs can occur, typically due to local or systemic infection with live BCG. These uncommon events include BCG sepsis, granulomatous prostatitis, granulomatous epididymo-orchitis, allergic reaction, contracted bladder, hepatitis, and pneumonitis. They require discontinuation of BCG and, usually, rapid initiation of antituberculous therapy.[13]

A number of other potential problems make BCG a suboptimal therapy. Some 30% to 45% of patients do not respond completely, and of those who do, up to 50% will have a recurrence with substantial risk of progression to MIUC.[14] Furthermore, up to 20% of patients cannot tolerate BCG because of AEs.[14] Healthcare workers are also at risk because of the use of live bacterium. Finally, issues associated with the BCG manufacturing process have complicated matters by creating a worldwide shortage.

While the mechanisms of BCG are not fully understood, it is known that BCG is internalized by urothelial cells and bladder cancer cells, some of which can be killed by direct BCG-related toxicity. In addition, internalized BCG induces production of proinflammatory cytokines that recruit immune effector cells, including CD4+ T cells, CD8+ T cells, and natural killer cells. These cells are a major source of Th1 cytokines that induce cytotoxic killing of cancer cells. Thus, response to BCG requires an intact immune system.[13,15,16]

Immune Checkpoint Inhibitor Therapy

Background

The mechanism of checkpoint inhibitors is much different from that of BCG and warrants a brief review of cancer immunology. To distinguish self from nonself, the immune system relies on T-cell receptors recognizing and binding to antigens presented by a protein complex called the major histocompatibility complex (MHC) on the surface of antigen-presenting cells (APC) (Figure 1).[17] However, the MHC presents self-antigens as well as foreign antigens, and T cells need to distinguish those they should attack. When the CD28 protein on the T cell binds to the B7 protein on the APC, the T cell is stimulated.

Once activated, T cells upregulate expression of cell-surface proteins called "immune checkpoints" that help to control immune response. When engaged with their ligands, checkpoint proteins modulate T-cell activation, Th1 cytokine production, and cell-mediated cytotoxicity. This physiologic "braking" of the immune system is important because it prevents unchecked inflammation and autoimmunity. In a cancer patient, however, it can allow tumor cells, which would normally be recognized by T cells, to evade the immune system.

A large number of checkpoint proteins have been identified, and to date, drugs that inhibit 2 of them, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), have demonstrated significant clinical activity. These proteins are thought to operate at different stages of an immune response (Figure 1). CTLA-4 is considered the lead checkpoint, because it stops initial T-cell activation, typically in lymph nodes. The PD-1 pathway is located in the tumor microenvironment, where it dampens ongoing immune responses after T cells have been activated. Unlike CTLA-4, which is expressed only on T cells, PD-1 is expressed on a broad range of cells, including activated and "exhausted" (nonfunctional) T cells, tumor-infiltrating T cells, and APCs, such as B cells, dendritic cells, and macrophages.

Mechanisms of Checkpoint Inhibition

CTLA-4 Blockade. As explained above, for a T cell to become fully activated, the B7 molecule on the APC must bind to the CD28 receptor on the partially activated T cell (Figure 1). Expression of CTLA-4 on a T cell interferes with this process, in that CTLA-4 outcompetes CD28 and binds with B7, which results in downregulation of T-cell activity. Monoclonal antibodies against CTLA-4 block the interaction between CTLA-4 and its B7 ligands, allowing activation of more T cells.

PD-1 and PD-L1 Blockade. The PD-1 pathway consists of the PD-1 receptor and its 2 ligands, PD-L1 and PD-L2. Both PD-1 and