New Strategies in Bladder Cancer: A Second Coming for Immunotherapy
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Abstract
Urothelial bladder cancer (UBC) remains one of the most common and deadly cancers worldwide, and platinum-based chemotherapy, which has been the standard-of-care in metastatic bladder cancer, has had limited success in improving outcomes for patients. The recent development and translation of therapeutic strategies aimed at harnessing the immune system have led to durable and prolonged survival for patients with several different cancers, including UBC. In this review, we discuss new findings in bladder cancer immunotherapy, including recent successes with immune checkpoint blockade. We also discuss therapeutic cancer vaccines and highlight several additional immunotherapy modalities in early stages of development.

Background
Urothelial bladder cancer (UBC) is the sixth most common cancer in the United States, with 74,690 cases diagnosed and 15,580 deaths in the year 2014. Similar to many cancers, it is a disease of the elderly, with a median age of 73 years at diagnosis (1). Risk factors for the development of bladder cancer include cigarette smoking and exposure to cyclic chemicals, dyes, rubbers, textiles, and paints (2). Smoking is the number one environmental risk factor and may be associated with the relatively high mutation rate noted in UBC (3, 4).

Approximately 70% of bladder cancers are diagnosed when they are non-muscle-invasive (NMIBC; ref. 5). For these tumors, transurethral resection of bladder tumor is the standard of care and aids in proper staging of the disease. For more advanced (muscle-invasive disease), the last major therapeutic advance was the introduction of platinum-based chemotherapy almost 30 years ago (6). For patients with advanced UBC, treatment options are limited and often ineffective, and outcomes remain poor (7, 8). Furthermore, for patients for whom first-line chemotherapy is not successful, no clearly defined second-line option exists and none have definitively been shown to prolong overall survival (OS; refs. 9, 10).

Recent understanding of the genomic alterations underlying bladder cancer have not yet led to new targeted therapies, but these insights show UBC to be a cancer with high somatic mutational burden (11). Mutations can provide neoantigens that can be recognized by the immune system (12). Indeed, a higher mutational load has been correlated with better response rates to immune checkpoint blockade in patients with lung cancer and melanoma (13, 14). These observations and the historically poor performance of current therapies in UBC provide a unique opportunity for the use of immunotherapy. Although a number of excellent reviews have recently described emerging data in tumor immunology (15–17), the focus of this review is to more specifically highlight recent advances in immunotherapy for UBC. Consequently, this review first provides a brief overview of conventional immunotherapy for UBC [bacillus Calmette–Guérin (BCG)], and then discusses immune checkpoint blockade as well as agonists and vaccines intended to initiate an antitumor immune response.

BCG is an attenuated form of the bovine tuberculosis bacterium Mycobacterium bovis. The first clinical trial of BCG in bladder cancer in 1980 showed a 20% reduction in recurrence rate (18). Despite its long history, the mechanism of action of BCG is not yet fully understood and is beyond the scope of this article but has recently been reviewed (19, 20). Clinically, randomized controlled trials (RCT) have shown that in NMIBC, BCG immunotherapy reduces rates of recurrence and progression while positively affecting mortality. RCTs comparing monthly, quarterly, and biannual BCG maintenance showed no sign of increased efficacy compared with induction BCG alone (21–23); however, the 3-week maintenance schedule of the Southwest Oncology Group demonstrated significant benefit with a 76.8-month recurrence-free survival duration (RFS) in the maintenance arm of the study compared with 35.7 months with induction therapy alone (24). The 5-year survival rate was 78% with induction therapy alone compared with 83% with maintenance. Thus, only 3-week BCG maintenance has been shown in RCTs to reduce disease progression and improve overall and disease-specific mortality (24, 25). Three-week maintenance BCG has also been shown to be superior to maintenance with epirubicin chemotherapy and combination treatment with epirubicin and IFNα (25, 26). Intravesical BCG immunotherapy remains the gold standard for the treatment of...
NMIBC, and exciting possibilities exist for improving outcomes in patients with superficial disease by combining BCG with other immune-modulatory therapies (Table 1).

**On The Horizon**

**Immune checkpoint blockade**

The genetic alterations that occur during carcinogenesis provide numerous antigenic targets that can be recognized by the immune system (12). However, cells of the adaptive immune system are often inhibited by pathways that are dysregulated in tumors and act to suppress their effector functions (27). Over the past 20 years, we have gained greater understanding of these pathways, which are mediated by cell surface molecules collectively termed ‘immune checkpoints.’ These entities represent a group of functionally related but biologically distinct cell surface receptors with important physiologic roles in maintaining self-tolerance, modulating the immune response to pathogens, and preventing autoimmunity (28, 29). Blocking antibodies targeting immune checkpoints have shown promise in several cancers, including melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma, and bladder cancer (30–33).

**CTLA-4: the first immune checkpoint.** CTL-associated antigen 4 (CTLA4) was the first immune checkpoint for which blockade was shown to enhance antitumor immunity (34). Because CTLA-4 functions by dampening T-cell activation, blocking of CTLA-4 enhances T-cell activation. This process is complex; normally, T-cell activation requires two signals; the first is a signal delivered when the T-cell receptor recognizes its specific antigen. A second signal is required for full T-cell activation; this signal 2 is delivered when B7 molecules on a mature dendritic cell (DC) bind to CD28 on the partially activated T cell. T-cell expression of CTLA-4 hijacks this process, binding with high affinity to B7 molecules and preventing the T cell from receiving signal 2 (Fig. 1; ref. 35). In patients, administration of anti-CTLA-4 leads to increased T-cell activation, a significant rate of objective responses, and a considerable rate of immune-related adverse events (irAE; refs. 36, 37).

In that regard, the rate of irAEs induced by CTLA-4 blockade is higher than that observed in patients treated with agents that block the checkpoint mediated by the interaction between PD-1...
is present in abundance in multiple tissue types including the skin, gut, liver, and others. PD-L1 (CD274), by contrast, is not constitutively expressed; expression is limited to tumors and to areas of active inflammation, where the PD-1/PD-L1 interaction likely serves to downmodulate an immune response during the effector phase (42).

In addition to being FDA approved for melanoma (43), CTLA-4 blockade has also been evaluated in a small number of bladder cancer patients. In a study of 12 patients with localized UBC who received neoadjuvant ipilimumab at a dose of either 3 or 10 mg/kg prior to cystectomy, the drug was shown to be safe and led to an increase in CD4 and CD8 T cells in both tumor and blood (44). A second phase II trial recently completed accrual of 36 patients; this single-armed study (NCT01524991) treats patients with standard first-line chemotheraphy (gemcitabine and cisplatin) in addition to ipilimumab (Table 1). The primary endpoint is 1-year survival. Although efficacy data are not yet available, interim analyses show an on-treatment increase in CD4 and CD8 T cells with an enhanced inflammatory cytokine signature including IL2, IL12, and granulocyte-macrophage colony-stimulating factor (GM-CSF; ref. 45). Although CTLA-4 is clearly an important immune checkpoint, moving anti–CTLA-4 into earlier-stage UBC or into combination regimens may be limited by its toxicity profile (46).

**PD-1/PD-L1: the next generation checkpoint.** The programmed death-1 (PDCD1; PD-1) pathway has emerged as an exciting therapeutic target in cancer therapy (27). Although CTLA-4 serves to inhibit T cells at the initial activation step, PD-1 appears to function by downregulating ongoing immune responses at sites of infection, that is, either in the periphery or in the tumor parenchyma (47). PD-1 is expressed during initial T-cell activation, and remains upregulated on exhausted, nonfunctional cells (48), and signaling occurs through binding of its major ligand partners PD-L1 (CD274 or B7-H1) and PD-L2 (CD273 or B7-DC; Fig. 1). Although there are similarities in the signaling of PD-1 and CTLA-4, clinical data show these pathways play nonredundant roles in inhibiting immune responses (49, 50).

Multiple studies showed that UBC expresses PD-L1 at similar levels to other tumors (approximately 10%–20% of tumor cells) with increased levels of PD-L1 expression seen in more advanced and metastatic tumors compared with early-stage disease (33, 51–55). Moreover, increased PD-L1 expression in these tumors has been associated with reduced OS and RFS following cystectomy. These data support the notion that bladder tumors may evade the immune system by upregulating PD-L1 expression. In the past year, exciting data have emerged from clinical trials of agents that block the PD-1/PD-L1 interaction. In a cohort of UBC patients in a phase I study, the activity of MPDL3280A (atezolizumab; Genentech, Inc.), a humanized IgG1 antibody against PD-L1, was examined. The overall response rate (ORR) was 35%, and the drug was well tolerated, with no treatment-related deaths and a 5% rate of grade 3–4 irAEs. The ORR was 43% in patients who were IC2/3 for PD-L1 expression on immune cells, whereas patients with lower levels of PD-L1 expression (IC0/1) had an ORR of 11%, suggesting that PD-L1 expression might serve as a weak predictive biomarker for treatment response (33). Overall, 55% of patients showed a reduction in tumor burden by RECIST criteria and responses were rapid, occurring at a median of 42 days. On the basis of these data, atezolizumab was granted Breakthrough Therapy Designation by the FDA in May 2014. A single-arm phase II trial of atezolizumab evaluating the efficacy and safety in patients with locally advanced and metastatic UBC who are treatment naïve and ineligible for platinum-based chemotherapy or who have progressed on a platinum-based regimen has accrued (NCT02108652), although efficacy data are not yet available. Anti-PD-1 (pembrolizumab; Merck) has also been evaluated in a relatively small cohort (N = 33) of patients with UBC. The ORR was similar to that for PD-L1 blockade at 28% (56). Median PFS and OS durations for UBC patients were 2 months and 12.7 months, respectively. As expected, PD-L1 expression correlated with response; patients in whom tumor and tumor-infiltrating immune cells were PD-L1 negative had a 0% ORR in contrast to patients that were PD-L1 positive who had a 29% ORR. A second-line phase III study comparing pembrolizumab treatment to paclitaxel, docetaxel, or vinflunine in patients with metastatic or unresectable UBC is now recruiting patients (NCT02256436). It should be noted that the favorable safety profile of PD-1 and PD-L1 blocking antibodies may play an important role in their development in UBC; approximately 48% of patients forgo chemotherapy in the second-line setting due to its relatively limited clinical benefit (57).

In UBC, PD-L1 status is emerging as a possible predictive biomarker. However, there has been great variation in the assay used to measure PD-L1 status to date (58). Sources of variation include the use of at least four different PD-L1 antibody clones; staining positivity cutoffs ranging from 1% to 10% and inclusion of tumor cells, immune cells, or both in the PD-L1 status. The standardization of antibodies, cutoffs, biopsy types, and analysis techniques will greatly aid in achieving a better understanding of the role of this dynamic biomarker in predicting responses to therapy.

Patients with PD-L1–positive tumor and tumor-infiltrating immune cells had response rates ranging from 29% to 43%. Thus, among patients with high PD-L1 expression, a sizeable proportion did not respond to treatment. An understanding of the determinants of response to PD-1/PD-L1 blockade is critically important for increasing the proportion of responding patients. Interactions among members of the tumor microenvironment, including tumor-associated macrophages (TAM), vascular endothelial cells, cancer-associated fibroblasts, and immunosuppressive metabolites such as kynurenine can all play an important role in dictating the level of T-cell infiltration in the tumor (17). Tumor-intrinsic mutations in the β-catenin pathway have been demonstrated to mediate cancer immune evasion and resistance to anti–PD-L1 therapy (59).

**B7-H3: highly expressed, but less clear in function.** B7-H3 (CD276) is a member of the B7 family of cell surface receptors whose expression can be induced on activated DCs, macrophages, T cells, B cells, and natural killer (NK) cells (Fig. 1; ref. 60). Its role in antitumor immunity is complex, with both stimulatory and inhibitory functions reported (61, 62). The receptor for B7-H3 remains unidentified as well. Nevertheless, targeting B7-H3 may be particularly important in UBC as reports have shown between 58% and 70% of tumors express this molecule (53, 54). An IgG1
Activation

OX40L
OX40
4-1BB
B7-H3 (ligand unknown)
CD40
CD80/86
TCR
CD28
CTLA-4
MHC I

PD-L1
PD-L1
PD-L2
CSF1R
Tryptophan Metabolites
IDO1
M2 (suppressive)
CSF1
IL34
PD-1
Pembrolizumab (anti–PD-L1)
Atezolizumab (anti–PD-L1)
MGA271 (anti–B7-H3)

Vaccines
BCG
Vesigenurtacel-L
Lapuleucel-T

Agonist antibodies
MEDI6469 (anti–OX40)
BMS-663513/PF05082566 (anti–4-1BB)
CP-870,893 (anti–CD40)

Monoclonal antibodies
Ipilimumab (anti–CTLA-4)
MGA271 (anti–B7-H3)

Small-molecule inhibitors
PLX3397 (CSF1R inhibitor)
FPA008 (anti–CSF1R antibody)
Emactuzumab (anti–CSF1R antibody)
INCBO24360 (IDO1 inhibitor)
GDC919 (IDO1 inhibitor)

Suppression

Agonist antibodies
MEDI6469 (anti–OX40)
BMS-663513/PF05082566 (anti–4-1BB)
CP-870,893 (anti–CD40)

Monoclonal antibodies
Ipilimumab (anti–CTLA-4)
MGA271 (anti–B7-H3)
antibody against B7-H3 has been developed (MGA271, Macrogenics, Inc.; ref. 63), and is now in a phase I clinical trial enrolling patients with a variety of advanced cancers including UBC (NCT01391143; Table 1).

Cancer vaccines

Cancer vaccines aim to initiate T-cell responses against tumor antigens by inducing activated antigen-presenting cells (APC) that express a tumor-associated or specific antigens (64). Activated APCs then drive the proliferation and function of specific T cells, which have the potential to mediate tumor cell lysis. Historically, vaccine approaches to cancer treatment have been limited by T-cell exhaustion, an altered differentiation state which manifests as a progressive and hierarchical loss of effector functions and upregulation of multiple inhibitory checkpoint molecules on the T-cell surface (48). The success of checkpoint molecule inhibitors in reversing T-cell exhaustion has important implications for the use of therapeutic cancer vaccines in the clinic. Several vaccines are under evaluation in UBC. In this section, we highlight two recent approaches.

A tumor cell–based vaccine: vesigenurtacel-L. Vesigenurtacel-L (Heat Biologics, Inc.) is an example of a cell-based vaccine; these types of vaccines have the theoretical advantage of presenting a number of tumor-associated antigens simultaneously (65). To generate this vaccine, an allogeneic bladder cancer cell line was modified to secrete the endoplasmic reticulum chaperone protein gp96 (HSP90B1). gp96 has two immunologically relevant biologic functions: (i) it chaperones peptides generated by intracellular proteosome degradation into class I MHC; and (ii) gp96 released from cells can function as a danger-associated molecular pattern and activate DCs by binding to TLR-2 and TLR-4 (66). Mechanistically, this vaccine is thought to function when gp96 released from dying vaccine cells binds to CD91 on host APCs, triggering endocytosis, and import of tumor cell antigens, which are subsequently presented to CD8 T cells in the context of class I MHC. A first-in-human trial of a similar vaccine in NSCLC demonstrated this approach to be safe, with 7 of 18 patients showing stabilized tumor growth though none displayed an objective response (67). A phase I/II trial in UBC (NCT02010203) has recently started accruing patients. After an initial safety run-in, this combination trial will quantifiably assess 1-year disease-free survival in patients with earlier-stage disease (NMIBC) treated with BCG plus vesigenurtacel-L (Table 1).

A DC-based vaccine: lapuleucel-T. As vaccine responses are driven by DCs, the most potent APC, one approach to cancer immunotherapy is to generate DCs ex vivo, load them with a tumor-associated antigen, and then administer the cells to patients (68). Lapuleucel-T (Dendreon) is an example of this approach in UBC; the vaccine is prepared by isolating peripheral blood monocytes from an individual patient, then culturing those cells with proprietary fusion protein that combines a tumor antigen (in this case HER2/neu) with GM-CSF, which serves to mature the peripheral blood mononuclear cells into antigen-presenting DCs. In a phase I study of 18 patients with HER2/neu–expressing tumors, immune responses to the target antigen were noted, the therapy was well tolerated, and 2 of 18 patients experienced stable disease lasting >48 weeks (69). This vaccine is now in a phase II trial evaluating survival, safety, and immune responses in the adjuvant setting in patients with high-risk HER2+ UBC (NCT01353222; Table 1).

Agonist antibodies: activating immune cells via costimulatory molecules

In addition to immune checkpoint molecules, whose engagement downregulates T-cell function, a number of molecules provide a positive signal to T cells, and the ultimate outcome of a T cell’s interaction with an APC involves an integration of both the positive and negative signals present during that interaction (Fig. 1). Although still in early stages of development, agonist antibodies that activate immune cells have tremendous potential in UBC and are introduced here with an eye toward future advancements.

OX40 on T cells. A member of the TNF receptor superfamily, OX40 (TNFRSF4, CD134) is a cell-surface molecule expressed when either CD4 or CD8 T cells recognize their specific antigen (70). Engagement between OX40 on a T cell and OX40 ligand on an APC provides a powerful costimulatory signal to the T cell (71). Not only does OX40 provide a stimulatory signal to effector T cells, it may also provide an inhibitory signal to regulatory T cells (ref. 72; Fig. 1). In a phase I study of a murine anti-OX40 (MED16469; Medimmune) in patients with advanced cancer, the drug had an acceptable safety profile and induced the regression of at least one metastatic lesion in 40% of patients (73). This murine anti-OX40 is now in clinical trials in combination with chemotherapy and radiotherapy in prostate cancer (NCT01303705) and breast cancer (NCT01862900) and in combination with anti–CTLA-4 in metastatic melanoma (NCT01689870). A second anti-OX40 antibody (MOX09016; Genentech, Inc.) is undergoing phase I testing in patients with advanced cancer (NCT02219724).

4-1BB on T cells. Like OX40, 4-1BB (TNFRSF9) is also a member of the TNF receptor superfamily, and is expressed on NK cells and activated T cells (71). Its ligand, 4-1BBL (TNFSF9), is expressed on activated APCs, and its engagement by 4-1BB leads to increased proliferation and expression of antiapoptotic molecules in T cells (Fig. 1). In an initial phase I study, an agonist 4-1BB antibody (BMS-663513, urelumab; Bristol-Myers Squibb) was well tolerated in patients with metastatic melanoma, and while only 6% of patients had a partial response, 17% of patients showed stable disease at 6 months (74). On the basis of these results, a
phase II trial was launched but patients experienced severe hepatitis and the trial was discontinued (75). A different 4-1BB antibody, PF05082566 (Pfizer Inc.) is currently being investigated in three phase I trials in combination with pembrolizumab (NCT02179918) or anti-CCR4 (NCT02444793; mogamulizumab, Kyowa Hakko Kirin) in advanced solid tumors, and rituximab for Hodgkin lymphoma (NCT01307267). Urelumab has also reentered clinical testing and is now being investigated in multiple phase I and II clinical trials in a variety of hematologic and solid malignancies.

**CD40 on APCs.** Unlike OX40 and 4-1BB, CD40 is predominantly expressed on APCs, and ligation of CD40 by its ligand CD40L, which is expressed on CD4 T cells, leads to stimulation and maturation of DCs (Fig. 1; ref. 76). Consequently, this is an indirect mechanism by which CD8 T-cell activation can be achieved (77). In a phase I study in patients with stage III and IV solid tumors, CP-870,893, an anti-CD40 agonist antibody, was well tolerated with 14% of patients showing a partial response (78). Trials evaluating CP870,893 in combination with anti–CTLA-4 (NCT01103635), and paclitaxel and carboplatin (NCT00607048) have been recently completed and future trials are anticipated.

**Targeting the tumor microenvironment in UBC**

**CSF1R.** CSF1R (CSF1R) is a cell surface receptor expressed predominantly on macrophages and monocytes (79). This agent may be important in UBC because macrophages exist on a continuum from an M1 (inflammatory) to an M2 (pro-tumorigenic) phenotype and the presence of M2 macrophages in the UBC stroma has been associated with BCG immunotherapy failure (80). CSF1 ligation promotes the skewing of macrophages to the M2 phenotype, so blocking CSF1, or depleting CSF1R-expressing cells promotes the development of antitumor M1 macrophages, and has been shown to be efficacious in animal studies (81). A relatively specific small-molecule inhibitor of CSF1R (PLX3397; Plexxikon) is now undergoing clinical evaluation in a phase I/II trial in combination with pembrolizumab in patients with advanced cancers including UBC (NCT02452424; Table 1). mAbs targeting CSF1R have also been generated (FPA008, Five Prime Therapeutics; emactuzumab, Hoffmann-La Roche). Targeting TAMs represents a potentially important alternative approach to tumor immunotherapy, particularly in combination with T-cell–directed agents like anti–PD-1/PD-L1 (Table 1).

**IDO1: a metabolic approach to T-cell dysfunction.** Indoleamine 2,3-dioxygenase 1 (IDO1) is a cytosolic enzyme that mediates the rate-limiting step of tryptophan metabolism (82). In the tumor microenvironment, it is expressed by myeloid-derived suppressor cells and TAMs in response to inflammation (83). T cells are critically dependent on tryptophan for their activity, and the catabolism of tryptophan by IDO1 profoundly suppresses T-cell activity (84). The small-molecule INC8024360 (Incyte Corp.) is a selective IDO1 inhibitor currently in phase I and II trials. A number of combination trials are under way, including NCT02178722, which combines INC8024360 with pembrolizumab for treatment in a number of diseases including UBC. Other IDO inhibitors are also in development, including indoixomod and GDC919 (Genentech, Inc.). Indoixomod has been tested in a variety of cancers including a phase II trial in refractory metastatic prostate cancer (NCT01560923). NLG919 is now in phase I trials, including a trial in combination with atezolizumab that includes UBC patients (NCT02471846; Table 1).

**Combination therapy**

Checkpoint blockade will likely change the shape of the UBC treatment landscape in the very near future, but it is clear from existing data that the majority of patients will not respond to monotherapy. Several rational strategies to address that issue are emerging. First, based on exciting clinical data in melanoma (49) and kidney cancer (85), combined checkpoint blockade is being evaluated in a variety of tumor types including UBC. A second strategy involves inducing a tumor-specific immune response via vaccination or intratumoral injection of immune-activating agents, including viral vectors (86). In UBC, a phase II trial of intravesical adenoviral-mediated IFNα gene therapy recently reported 10 of 34 patients experiencing a complete response at 12 months (87). This trial is currently ongoing. It should be noted, however, that an influx of activated IFNγ-secreting T cells into a tumor is generally accompanied by an upregulation of PD-L1 on the tumor cells, a process termed “adaptive immune resistance” (88) that suggests that vaccines might be most effective when combined with a PD-1/PD-L1 blocking agent. Clinical trials are currently under way in UBC testing combinations of checkpoint blockade and chemotherapeutics, vaccine approaches, tyrosine kinase inhibitors, tumor microenvironment and myeloid cell targeting therapies, and metabolic enhancement strategies (Table 1).

Moving forward, the design of such strategies will require a thorough understanding of the determinants of the tumor immune environment in UBC.

**Conclusions**

In a malignancy in which no major treatment advances have occurred in the past 30 years, we are now witnessing a second coming of immunotherapy in the form of PD-1/PD-L1 blockade. However, modern immunotherapy is still in its infancy in UBC; in addition to immune checkpoint blockade, a number of new metabolic, vaccine, agonist, and tumor microenvironmental approaches are in development. Ultimately, the application of these agents in UBC should be driven by a more comprehensive understanding of the factors limiting an antitumor immune response, both in patients and in physiologically relevant animal models.

**Disclosure of Potential Conflicts of Interest**

N.M. Hahn is a consultant/advisory board member for AstraZeneca/MedImmune, Bristol-Myers Squibb, Genentech/Roche, Merck, and OncoGenex Pharmaceuticals. C.G. Drake reports receiving commercial research grants from Aduro Biotech, Bristol-Myers Squibb, and Janssen; has ownership interest (including patents) in Compugen, NexImmune, Potenza Therapeutics, and Tizona Therapeutics; and is a consultant/advisory board member for Agenus, Argos Therapeutics, Bristol-Myers Squibb, CompuGen, F-star Biotechnology [uncompensated]. Jansen, and MedImmune. No potential conflicts of interest were disclosed by the other authors.

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