New Understandings in Bladder Cancer and the Role of the Immune System

Immune-Based Approaches to Disease Management
Abstract

Bladder cancer is the fifth most commonly diagnosed cancer in the United States. Despite local treatment options, bladder cancer is associated with high rates of recurrence and progression, and the 5-year survival among patients with metastasis is one of the lowest among cancers at 5%. Urothelial bladder cancers (which make up the vast majority of bladder cancers) are considered immunogenic and produce neoantigens—molecules that are recognized by the immune system and required for induction of an antitumor response. Bladder cancers also express several ligands that can inhibit effector T-cell function that allows for evasion of an antitumor immune response. More than 40 immune-based approaches that aim to reactivate the antitumor immune response are under active investigation in advanced bladder cancer.

Unmet Needs in Managing Bladder Cancer

Bladder cancer is the fifth most commonly diagnosed cancer in the United States, with an estimated 76,960 new cases in 2016, representing 4.6% of all new cancer diagnoses. The lifetime risk of developing bladder cancer is 2.4%, based on 2010–2012 data. Diagnosis likelihood increases with age, peaking in patients aged 75 to 84 years (mean age at diagnosis, 73 years). Incidence and mortality is higher in men than women (58,950 vs 18,010 new cases or >3-fold increase and 11,820 vs 4,570 deaths, respectively).

Urothelial carcinoma

The vast majority of bladder cancers, approximately 90%, are urothelial in origin and referred to as urothelial cell carcinoma or transitional cell carcinoma. Urothelial carcinomas can also arise from the urothelium of renal pelvis, ureters, and urethra. Other less common histologic types of bladder cancer include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, sarcoma, and some rare neoplasms.

Disease staging for bladder cancer is largely based on level of invasion of the bladder wall. Figure 1 illustrates staging according to the tumor-node-metastasis (TNM) system, characterized by invasion through the bladder lumen and lamina propria (non–muscle-invasive bladder cancer, NMIBC), into the inner and outer muscle (muscle-invasive bladder cancer, MIBC), and to distant structures (metastatic bladder cancer, mBC). Although NMIBC is characterized by frequent recurrence and high morbidity but a low risk of mortality, MIBC is potentially lethal in approximately 50% of cases overall. Papillary NMIBC is thought to develop via epithelial hyperplasia and recruitment of a branching vasculature, whereas MIBC is proposed to develop via flat dysplasia and carcinoma in situ (Tis).

Despite local treatment options, recurrence is common

An estimated 587,000 people are living with bladder cancer in the United States (2013 data). Overall survival with bladder cancer has remained consistent during the past 3 decades. There is an estimated 16,390

Key Points

- Bladder cancer is the 5th most common cancer
  - High mortality rates
  - 5-year survival rates for metastatic disease ~5%
  - Despite local treatment options, recurrence common, progression rates high
Recurrence rates are high in bladder cancer, which necessitates lifetime surveillance and repeated treatment of recurrent disease. Patients with NMIBC face probability of recurrence within 5 years of 50% to 90%, depending upon stage, with flat Tis most likely to recur (Table 1). Progression to invasive disease has been reported in up to 40% of cases. Patients who present with or progress to advanced bladder cancer face a poor prognosis, and mortality rates in this population have not improved during the last decade.

Table 1. Approximate probability of recurrence for NMIBC

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Probability of recurrence in 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta, low grade</td>
<td>50</td>
</tr>
<tr>
<td>Ta, high grade</td>
<td>60</td>
</tr>
<tr>
<td>T1, low grade (rare)</td>
<td>50</td>
</tr>
<tr>
<td>T1, high grade</td>
<td>50–70</td>
</tr>
<tr>
<td>Tis</td>
<td>50–90</td>
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</table>

Further, patients affected by bladder cancer may present with comorbidities due to advanced age, which may limit treatment options.
Current Management of Bladder Cancer

Clinical management of bladder cancer follows 3 approaches, based on extent of disease. Treatment of NMIBC involves surgical removal of the lesion, with use of intravesical bacillus Calmette-Guérin (BCG) therapy as needed. The central management decisions in MIBC are, first, whether to perform a cystectomy or bladder-preserving treatment (in a select group of patients) and, then, whether systemic therapy is needed to address the risk of metastases. Finally, treatment of metastatic bladder cancer (mBC) aims to prolong quantity and quality of life. Thus, for the majority of patients, surgery remains the mainstay of bladder cancer management. While several chemotherapeutic regimens have demonstrated some activity, there has been little advancement of systemic agents for bladder cancer during the last couple of decades (Figure 2). Recently, however, immunotherapy has emerged as a new approach for the treatment of bladder cancer. Optimal management of MIBC and mBC requires a multidisciplinary approach (Figure 3). Treatment decisions are best made by either a multidisciplinary...
tumor board or directed consultations between specialists. Primary care may be provided by a urologist, but a radiation oncologist may be consulted in bladder-preserving resection or for palliative care. A medical oncologist may be involved in neoadjuvant chemotheraphy or palliative care and is mainly responsible for treatment of advanced disease. Oncology nurses and pharmacists also play key roles in treating bladder cancer patients. Last, a pathologist is essential for complete evaluation, including biomarker testing.6,23-26

**Treatment recommendations in MIBC and mBC**

Radical cystectomy remains the primary treatment for MIBC (T2-4a, N0M0), recommended by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO). Bladder preservation via use of chemoradiotherapy may be appropriate for select patients and is superior to radiotherapy alone. Neoadjuvant cisplatin-based chemotherapy, or adjuvant chemotherapy in patients who did not receive neoadjuvant chemotherapy, is recommended. In patients ineligible for cisplatin-based chemotherapy, chemotherapy is only recommended if the goal is downstaging of surgically unresectable tumors.6,25 Treatment decisions are individualized based upon patient and disease factors. Importantly, decisions regarding bladder preservation or radical cystectomy in elderly/geriatric patients with invasive bladder cancer should be based on tumor stage, bladder function, and ability to tolerate major surgery, radiotherapy, and/or chemotherapy.25

Evidence shows, however, that nearly half of patients with MIBC are not treated with chemotherapy (Figure 4). The patient population affected by bladder cancer may present with comorbidities due to advanced age, which may limit treatment options.1,28 Further, survival following chemotherapy for advanced bladder cancer is poor, and does not appear to be influenced by regimen. A large trial comparing 2 standard chemotherapy (gemcitabine + cisplatin vs methotrexate/vinblastine/doxorubicin/cisplatin [MVAC]) regimens demonstrated comparable poor survival trends for both arms. Median survival was 14 to 15.2 months, and survival rate continued to decrease rapidly through the first 2 years (Figure 5).29

Patients who have progressed to metastatic bladder cancer may be considered for systemic therapy. In patients eligible for cisplatin-based therapy, preferred combination regimens include gemcitabine/cisplatin, MVAC, and high-dose MVAC with growth factor support. In those ineligible for cisplatin, carboplatin-based chemotherapy or single-agent chemotherapy may be considered. In the second-line setting, there is no Category 1 standard systemic regimen; thus, enrollment in clinical trials is encouraged. Single-agent therapy with the immunotherapy atezolizumab or the chemotherapy agents paclitaxel, docetaxel, gemcitabine, and pemetrexed may also be considered. Alternative regimens may be considered in select patients: Nab-paclitaxel, ifosfamide, or methotrexate as single agents, or combination regimens including gemcitabine with either ifosfamide plus doxorubicin, paclitaxel, or cisplatin or dose-dense MVAC.6

**Figure 4.** MIBC treatment patterns; percentage of patients (2013). Chemo includes targeted therapy and immunotherapy drugs; cystectomy, surgery that removes all or part of the bladder as well as the surrounding fatty tissue and lymph nodes.28
Figure 5. Kaplan-Meier survival curves for 2 standard chemotherapy regimens: GC and MVAC.²⁹

![Graph showing Kaplan-Meier survival curves for GC and MVAC.]

GC: median = 14.0 (12.3-15.5 m); 13.3% censoring
MVAC: median = 15.2 m (13.2-17.3 m); 15.4% censoring
HR: 10.9 (0.88-1.34)
Log-rank \( P = 0.44 \)
Wald’s \( P = 0.66 \)

Figure 6. Overview of systemic therapy options in bladder cancer.²⁵, ³⁰-³²

<table>
<thead>
<tr>
<th>NMIBC</th>
<th>Neoadjuvant/Adjuvant</th>
<th>1st-Line mBC</th>
<th>2nd-Line mBC</th>
<th>Next-Line mBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No systemic therapy</td>
<td>Gem + cisplatin; A-MVAC (cisplatin)</td>
<td>Gem + cisplatin; A-MVAC or Gem + carboplatin</td>
<td>Atezolizumab; Enrollment into a clinical trial; Paclitaxel; Docetaxel; Vinflunine</td>
<td>Paclitaxel; Docetaxel; Vinflunine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Carboplatin</th>
<th>Atezolizumab</th>
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<tbody>
<tr>
<td>ORR</td>
<td>50%-60%</td>
<td>36%</td>
<td>15%</td>
</tr>
<tr>
<td>Median OS</td>
<td>15 mo</td>
<td>9 mo</td>
<td>8 mo</td>
</tr>
<tr>
<td>1-y OS</td>
<td>60%</td>
<td>37%</td>
<td>37%</td>
</tr>
</tbody>
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Unmet Need
IO Refractory Patients

A-MVAC=accelerated methotrexate/vinblastine/doxorubicin/cisplatin; Gem=gemcitabine; ORR=objective response rate; OS=overall survival.
Role of Immune System in Advanced Bladder Cancer

Understanding of the role the immune system plays in combating bladder cancer continues to evolve. Bladder cancer is among tumor types with the highest mutational burden, third after lung cancer and melanoma (Figure 7). High mutational load may correlate with immunogenicity. Presence of mutations also provides valuable prognostic information in MIBC.

Reactivating the antitumor immune cycle

Activating the body’s own immune system against tumor cells has long been a goal in cancer management. Bladder represents one of the first cancer types to be treated with an immunologic approach, as local treatment with intravesical BCG represents the first Food and Drug Administration (FDA)-approved immunotherapy. BCG is an option for the management of high-grade Ta, T1, and Tis NMIBC.

An effective antitumor immune response relies upon many cell types and their various functions (Figure 8). Initiation of the cycle begins with release of antigens, which are captured by antigen-presenting cells such as dendritic cells (Step 1); antigens are then processed and complexed with major histocompatibility complex (MHC) on the cell surface (Step 2). Antigen-presenting cells travel to lymph nodes and bind to T cells leading to T-cell activation (Step 3). Activated T cells travel to and infiltrate the tumor bed (Steps 4 and 5), where they bind to and kill target cancer cells (Steps 6 and 7). Finally, additional tumor-associated antigens released at tumor cell death reinitiates the antitumor immunity cycle, increasing the breadth and depth of the response as the cycle continues. In patients with cancer, however, tumors may interfere with this cycle, preventing an appropriate immune response. Immunotherapies are designed to overcome suppression of the immunity cycle by the tumor and tumor microenvironment to reinitiate a self-sustaining antitumor immunity cycle.

Figure 7. Overall somatic mutation rates across cancers.

AML=acute myeloid leukemia; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; ESO AD=esophageal adenocarcinoma; GBM=glioblastoma multiforme; RCC=renal cell carcinoma.
**Figure 8.** The cancer immunity cycle.36,38,39

Antigen-specific naive T cells recognize the presented antigens and are activated, resulting in clonal expansion.

- **STEP 1:** Tumor antigens released by tumor cells captured by APCs.
- **STEP 2:** Antigens processed by APCs and presented on MHC molecules.
- **STEP 3:** Antigen-specific naive T cells recognize the presented antigens and are activated, resulting in clonal expansion.
- **STEP 4:** Activated T cells traffic to the tumor in the periphery.
- **STEP 5:** Effector T cells infiltrate into the tumor and tumor microenvironment.
- **STEP 6:** T cells interact with tumor cells and recognize antigens (effector phase).
- **STEP 7:** Antigen-specific T cells attack and destroy tumor cells.

**APC** = antigen-presenting cell; **MHC** = major histocompatibility complex.

**Figure 9.** Balance of costimulation and coinhibition in the immune response.36

- **ACTIVATING RECEPTORS:** CD28, OX40, GITR, CD137, CD27, HVEM.
- **INHIBITORY RECEPTORS:** CTLA-4, PD-1, TIM-3, BTLA, VISTA, LAG-3.

**BTLA** = B- and T-lymphocyte attenuator; **CTLA** = cytotoxic T-lymphocyte antigen; **GITR** = glucocorticoid-induced tumor necrosis factor receptor-related protein; **HVEM** = herpes virus entry mediator; **LAG** = lymphocyte-activation gene; **PD** = programmed cell death protein; **TIM** = T-cell immunoglobulin and mucin-domain containing; **VISTA** = V-domain Ig suppressor of T-cell activation.
Antigen-presenting cells present the neoantigen to the T cell via T-cell receptor/MHC interaction. The T cell must also be signaled to either respond to or ignore the antigen. This is accomplished by presentation of ligands by the antigen-presenting cells or other cells, which bind to receptors on the T cell. These receptors may activate or inhibit the T cell, and regulate the final T-cell response. Several surface proteins involved in T-cell function are members of the tumor necrosis factor receptor or B7 superfamilies (Figure 9). Importantly, T-cell modulation through inhibitory receptors by tumors may lead to T-cell exhaustion and immune evasion.

**Immune Checkpoints in bladder cancer**

PD-1 is a receptor located on the T cell and other immune cells when they are activated. When bound to either of its ligands (PD-L1 or PD-L2), PD-1 inhibits T-cell function (Figure 10). PD-L1 may be expressed on normal or tumor cells. The presence of PD-L1 on normal cells prevents host tissue damage/autoimmune response, whereas the presence of PD-L1 on tumor cells allows tumors to inhibit T-cell function, and thus evade an immune response. PD-L1 on the T cell has also been found to bind CD80 on the antigen-presenting cell (Figure 11). PD-L1 impairment prevents the PD-L1 interaction with CD80, potentially maximizing its availability to activate T-cells.

PD-L2 is a second ligand for PD-1. PD-L2 is primarily expressed on immune cells but also has expression on nonimmune cells, including vascular endothelium, lung epithelia, and placental cells. PD-L2 expressed on endothelial cells can inhibit effector T-cell activity and reduce tissue damage.

**Key Points**

- Bladder cancer is highly immunogenic
- Expresses high levels of neoantigens
- Expresses ligands (e.g., PD-L1) that can inhibit effector T-cell function and T-cell activation
Figure 12. Common toxicities associated with systemic chemotherapy particularly cisplatin-based therapy (top)\(^{46-50}\) and immuno-oncology therapy (bottom)\(^{51,52}\) in patients with advanced bladder cancer. Effects of cytotoxic chemotherapy on specific organ systems and the body as a whole are well characterized. Immune-related adverse reactions related to T-cell modulation may affect various organ systems, and adverse event monitoring and early identification of immune-mediated adverse events is crucial to safe use of immuno-oncology therapy.
Immune-Based Approaches Under Active Investigation in Advanced Bladder Cancer

Several immune-based approaches are being investigated as treatment for bladder cancer, including several approaches: innate immune cell activation, T-cell regulation, oncolytic viruses, and vaccines. Immune checkpoint inhibitors represent the most widely studied immune-based approach for management of bladder cancer. In May 2016, the first PD-L1 inhibitor was approved with 2 other checkpoint inhibitors also receiving breakthrough status this past year. There are at least 18 ongoing trials of monotherapy and 39 ongoing trials of combination regimens as of September 2016.

Clinical considerations: toxicities of systemic therapies

Recommended systemic therapies are associated with a range of toxicities, and the risk of treatment must be balanced against the potential benefit of treatment for each patient. Common toxicities associated with systemic chemotherapy, especially cisplatin, include mucositis, nausea, vomiting, alopecia, renal impairment, myelosuppression, vascular toxicity, ototoxicity, and peripheral neuropathy. Importantly, the common toxicities associated with chemotherapies differ from those associated with immunotherapy (Figure 12). The safety profile of checkpoint inhibitors in bladder cancer differs from chemotherapeutic agents, and toxicities include rash, laboratory abnormalities, pneumonitis/dyspnea, and colitis. Adverse event monitoring and early identification of immune-mediated adverse events is crucial to safe use of both chemotherapy and immuno-oncology therapy.

Key Points

- Immune-based approaches are being actively investigated
  - >40 immune-based trials in advanced bladder cancer underway
- The safety profile of checkpoint inhibitors in bladder cancer differs from chemotherapeutic agents, and toxicities include rash, laboratory abnormalities, pneumonitis/dyspnea, and colitis

Conclusions

Bladder cancer is the 5th most common cancer and its treatment represents a significant unmet medical need, due to common recurrence. Patients with MIBC and mBC have poor long-term survival, and there are no standard treatments for mBC. Patients with mBC have a 5-year overall survival rate of only 5%. Bladder cancer is a highly immunogenic cancer that expresses high levels of neoantigens and ligands, such as PD-L1, that can inhibit effector T-cell function and T-cell activation. The ability of bladder cancers to evade the antitumor immunity cycle may contribute to the high recurrence rate and aggressive nature of these tumors. More than 40 immune-based approaches are under active investigation in advanced bladder cancer.

References

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