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Emerging role of checkpoint inhibition in localized bladder cancer

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Abstract

Objective: Checkpoint inhibitors have rapidly become a standard treatment option for metastatic urothelial carcinoma. A wave of enthusiasm for these drugs has pushed them also into the setting of localized bladder cancer, including both non–muscle-invasive bladder cancer (NMIBC) and muscle-invasive disease bladder cancer (MIBC). Here, we aimed to review the emerging role of checkpoint inhibition in localized bladder cancer.

Methods: We reviewed the current treatment landscape for both NMIBC and MIBC and established a significant unmet clinical need for novel therapies. We have compiled the evidence that supports the investigation of checkpoint blockade in localized bladder cancer and have reviewed the corresponding clinical trial's landscape.

Results: The success of checkpoint inhibitors in metastatic bladder cancer offers the most compelling rationale for testing checkpoint blockade in localized disease. The established benefit of intravesical Bacillus Calmette–Guérin provides precedent for immune therapy in bladder cancer. Immune dysfunction has been described in bladder cancer, and we know that checkpoint molecules are expressed in these tumors. Furthermore, the high neoantigen burden of bladder cancer and results from preclinical studies suggest that checkpoint blockade deserves testing in earlier stage disease. Multiple trials are either planned or underway in almost all bladder cancer disease states.

Conclusion: Ongoing trials would determine in the next several years whether checkpoint inhibitors can have a similar effect in localized disease as they have had in metastatic bladder cancer. They would also determine if patients with earlier disease would tolerate the toxicity of systemic therapy. The future holds promise for predictive biomarkers to guide individualized use of these agents and for effective combination therapies to overcome resistances.

Keywords: Bladder cancer; Urothelial carcinoma; Immune therapy; Checkpoint inhibitors; Clinical trials

Introduction

Checkpoint inhibition has very recently been approved as a second-line systemic therapy for patients with metastatic and locally advanced bladder cancer. This represents a major breakthrough in a malignancy that has lacked new therapeutic agents for more than 2 decades. The enthusiasm for checkpoint inhibition as a form of immunotherapy has carried over into localized bladder cancer, where it is under investigation in multiple clinical trials. Localized bladder cancer includes non–muscle-invasive (Ta/Tis/T1) bladder cancer (NMIBC) and resectable, (T2–4aN0M0) muscle-invasive bladder cancer (MIBC). Advances in the treatment of these disease states have been equally sparse in the past 3 decades. Here, we aim to establish the rationale for studying checkpoint inhibition in localized bladder cancer and to highlight some of the ongoing clinical trials.

Non–muscle-invasive bladder cancer–defining disease states

Given the current limitations in our management of NMIBC, it is easy to postulate a role for checkpoint inhibition in this disease setting. A critical unmet need for these patients is the lack of efficacious second-line treatment options after failed Bacillus Calmette–Guérin (BCG) therapy. The relatively high rate of adverse events with

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Table 1
Non invasive bladder cancer disease state definitions

Disease state [53]	NMIBC risk category	Prior BCG	Special cases	Implications for trial design
BCG failure	Intermediate or high risk	Induction only; or last maintenance dose >6 mo previously		Additional BCG is an option Randomized trial of BCG vs. test agent ± BCG
BCG-unresponsive	High risk	Induction and at least 1 round of maintenance or second induction cycle; last dose <6 mo previously.	Any patient with high-grade T1 disease after induction only	Additional BCG is not an option Single-arm trial of novel agent alone

intravesical BCG further augments the need for new strategies for NMIBC.

One of the key obstacles to therapeutic advances in this disease setting has been the lack of standardized definitions of specific disease states. Consensus definitions have now evolved for both "BCG failure" and "BCG-unresponsive" high-risk NMIBC, which provide an important framework for clinical trial design (Table 1).

The treatment landscape for muscle-invasive bladder cancer

Standard therapy for localized MIBC is cisplatin-based neoadjvuant chemotherapy followed by radical cystectomy [1–6]. Trimodal therapy is a treatment option also in select patients. The urologic community has been slow to adopt neoadjuvant chemotherapy, so that adjuvant chemotherapy is more frequently administered in many centers. Although trial results support also the effectiveness of adjuvant chemotherapy, the data is considered less robust. Many patients are excluded from current perioperative chemotherapy owing to medical comorbidities or poor renal function [7,8]. Regardless of the timing of perioperative chemotherapy, even with an optimal multimodal approach, the 5-year overall survival rate of patients with MIBC is only approximately 50% [9].

The neoadjuvant paradigm is particularly attractive for drug development because abundant tissue is available from the transurethral resection of bladder tumor specimen to allow for assessment of potential enriching biomarkers, and further tissue is generally available after treatment in the form of the radical cystectomy specimen, which is useful for measuring pharmacodynamic end points [10]. Immediate clinical response can also be measured for down-staging at cystectomy [10]. An example of an innovative trial design using the neoadjuvant chemotherapy paradigm is the Southwest Oncology Group trial S1314. Here the COXEN algorithm is being tested to predict response to cisplatin-based neoadjuvant chemotherapy before radical cystectomy (NCT02177695).

Even with optimal neoadjuvant therapy, the need for effective adjuvant therapy will remain. For example, patients who receive neoadjuvant cisplatin-based therapy but have residual MIBC are at high risk for recurrence and mortality, but currently they have no good treatment options. An additional obstacle to timely delivery of adjuvant therapy is the high [11] complication rate associated with radical cystectomy. Clinical trials in the adjuvant setting for MIBC have proven challenging to complete successfully and have experienced poor accrual.

Recent advances in our understanding of the molecular landscape of MIBC, especially through the efforts of The Cancer Genome Atlas [12], provide an important foundation for the development of targeted therapies in bladder cancer. New insights into the biology and mutational burden of bladder cancer also suggest a critical role for immune regulation in some tumors [11]. Kardos et al. [13] recently reported a distinct claudin-low molecular subtype, which is characterized by a highly immunosuppressed tumor microenvironment in the presence of tumor immune infiltration. Rosenberg et al. have reported in the metastatic setting that the molecular subtypes are associated with response to the PD-LI inhibitor atezolizumab. In particular, the immune-infiltrated luminal tumors in cluster II demonstrated the best response [11].

The rationale for checkpoint inhibition in localized bladder cancer

T cells recognize unique tumor antigens on tumor cells and on antigen-presenting cells. In an effective antitumor immune response, cytotoxic T cells traffic to and infiltrate tumors, bind to tumor cells, and induce apoptosis. However, if the tumor-infiltrating immune cells express high levels of PD-L1, they would bind PD-1 on other T cells and remain inactive, thereby allowing the tumor to evade the immune response. The interaction of PD-1 and PD-L1 not only induces an inhibitory signal but also reduces cytokine production and proliferation of T cells.

The rationale for testing checkpoint inhibition in localized bladder cancer is based on a combination of several different components of evidence. The 2 most important factors are the known role of immune dysfunction in bladder cancer and the proven efficacy of checkpoint