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UROLOGIC ONCOLOGY

Seminars article

Recent developments in the treatment of advanced bladder cancer

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Abstract

Urothelial carcinoma of the bladder is a common malignancy which has historically been difficult to treat in its advanced stages. Clinically effective treatment options for locally advanced/inoperable or metastatic urothelial carcinoma (mUC) consisted of cisplatin-based chemotherapy regimens, with few other impactful therapeutic options. The past 2 years have seen a remarkable shift in the therapeutic landscape of mUC, with 5 novel immunotherapy agents receiving FDA approval for mUC, including first-line and second-line postplatinum settings. There are now many important clinical trials ongoing seeking to answer how best to use chemotherapy, immunotherapy, and targeted therapy agents in patients with mUC. Here we review the current standard of care for patients with mUC based on published data from the past 2 years, and look forward toward future research directions. © 2018 Elsevier Inc. All rights reserved.

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Background

Urothelial carcinoma (UC) of the bladder is one of the most common malignancies in the United States, with an estimated 79,030 new cases and 16,870 deaths in 2017 [1]. Approximately, 5% of patients have metastatic disease at the time of diagnosis, and of the approximately 30% of patients initially diagnosed with muscle-invasive disease, half will eventually develop metastatic disease [2]. For many years platinum-based chemotherapy was the only FDA approved treatment for locally advanced inoperable or metastatic UC (mUC). Until 2016 there was no approved postplatinum therapy for this disease, and response rates for second line single-agent chemotherapy regimens (e.g., taxanes) were approximately 10% with median survivals of 6 to 8 months [3,4]. However, over the past few years numerous clinical trials have demonstrated the clinical benefit of immunotherapy and the promise of targeted therapy for mUC. There are currently 5 immunotherapy agents (atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab), which have been approved in the United States for use postplatinum in mUC. Three drugs are approved in the European Union in this setting: atezolizumab, pembrolizumab, and nivolumab, 2 of which (atezolizumab and pembrolizumab) are approved for first-line treatment of patients with mUC who are ineligble for cisplatin. These are also approved in the European Union for the same indication. Large clinical trials of novel therapeutic agents will answer important questions regarding how best to sequence and combine immunotherapy, chemotherapy, and targeted therapies in patients with mUC. Here we provide an overview of the evidence supporting the new standard of care for patients with mUC, as well as a review of key ongoing clinical trials and future directions for research.

Single-agent immunotherapy postplatinum in the second line and beyond

Single-agent chemotherapy (e.g., paclitaxel, docetaxel, pemetrexed, and vinflunine) after disease progression following a first-line cisplatin-based regimen has historically yielded disappointing results, with objective response rates (ORRs) of approximately 10%. Bladder cancer has relatively high rates of somatic mutation, suggesting the possibility of increased immunogenicity via development

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of neoantigens [5]. Over the past 5 years new classes of drugs targeting various immune checkpoints have been developed and USFDA approved for a wide variety of malignancies [6]. One major checkpoint axis which has been targeted is the programmed death 1 (PD-1)/PD ligand 1 (PD-L1) signaling pathway; PD-1 is typically expressed on activated T cells, whereas PD-L1 can be expressed by a variety of cells, including tumor cells, antigen presenting cells, and other cells in the tumor microenvironment [7]. When PD-1 is bound to its ligand, inhibitory pathways are initiated which decrease the activity of the T cell; thus monoclonal antibodies (mAb) designed to target both PD-1 and PD-L1 have been developed, with the goal of reinvigorating the antitumor activity of T cells. In the past 2 years, 5 checkpoint inhibitors have been FDA approved in the United States for use in mUC which has progressed beyond platinum chemotherapy. These agents and the relevant clinical trials, which compared response rates of PD-1 and PD-L1 inhibitors to historic single-agent chemotherapy control rates of approximately 10%, are highlighted later.

Atezolizumab is a humanized IgG1 mAb which selectively binds PD-L1, and the first drug to obtain USFDA approval (May 2016) for the treatment of mUC postplatinum therapy. This approval was based on results from 1 arm of a large multicenter parallel phase II trial (IMvigor 210) investigating the activity of atezolizumab in patients with inoperable or mUC following platinum-based chemotherapy [8]. In total 310 patients were treated with atezolizumab 1,200 mg every 3 weeks, and the overall ORR was 15%, which achieved statistical significance ($P = 0.005$) compared with a historical control ORR of 10%. The investigators also reported response rates in patient cohorts defined by the percentage of immune cells (IC) PD-L1 staining positive for PD-L1 in the tumor microenvironment (IC0 [$<1\%$], IC1 [1%–5%], IC2/3 [$>5\%$]); patients whose tumors featured higher expression of PD-L1 on IC had the highest ORRs (e.g., IC2/3%–27%). Atezolizumab was safe and well-tolerated, with a grade 3/4 AE rate of 16%. In January 2017, the results of the phase III confirmatory study (IMvigor 211) which randomized patients with mUC and prior platinum therapy to atezolizumab or investigator's choice chemotherapy were reported. The study unfortunately did not meet its primary endpoint of improved overall survival (OS) in the IC2/3 (PD-L1 high expressing) group. Due to the hierarchical design of the study, no further analysis could be performed. The median OS was 11.1 months with atezolizumab vs. 10.6 months with chemotherapy, and though the response rate was the same for atezolizumab and chemotherapy (13%) atezolizumab demonstrated more durable responses and a lower incidence of adverse events compared to chemotherapy [9]. The data from this trial has not been published yet and currently atezolizumab has retained its approval in the second line and beyond setting.

Nivolumab is a fully human IgG4 mAb which targets the PD-1 receptor on T cells and has received FDA approval in numerous malignancies. In a multicenter phase II single arm trial 265 patients who received nivolumab 3 mg/kg every 2 weeks were evaluable for response; confirmed objective responses were noted in 52 patients (19.6%) [10]. These investigators also looked at response rates in separate cohorts of patients divided by PD-L1 expression in the tumor microenvironment; these groups were defined as PD-L1 $< 1\%$, PD-L1 $\geq 1\%$, and PD-L1 $> 5\%$. The ORRs in these groups were 28.4% (PD-L1 $> 5\%$, $n = 81$), 23.8 (PD-L1 $\geq 1\%$, $n = 122$) and 16.1% (PD-L1 $< 1\%$, $n = 143$). No optimal PD-L1 cutoff for clinical use was determined, as all groups experienced clinical activity. Nivolumab was tolerable with a treatment related grade 3/4 AE rate of 18%, which was comparable to data published from a phase I study in a similar population [11]. The median duration of response was not reached at the time of publication.

Durvalumab is an engineered human IgG1 mAb targeting PD-L1. In a phase I/II clinical trial, 191 patients with mUC who had progressed following, been ineligible for or refused platinum chemotherapy were enrolled [12]. Durvalumab treatment at 10 mg/kg every 2 weeks led to overall ORR of 32.1% among the 159 patients evaluable for response at the time of the analysis, including 7 complete responses (CR) (ORR was 17.8% in the "as-treated" population, $n = 191$). These investigators also reported responses by cohorts defined by the percentage of PD-L1 staining in the tumor microenvironment (PD-L1 "high" defined as $>25\%$ of either tumor cells (TC) or IC staining positive, PD-L1 "low" defined as $<25\%$ of TC and IC staining positive); the response rate was 27.6% in the PD-L1 "high" group and only 5.1% in the PD-L1 "low" or negative group. CRs were noted in the PD-L1 "low" group, and responses in both groups had similar durability. Durvalumab was tolerable, with 6.8% of patients experiencing a treatment related grade 3 or 4 adverse event (AE), similar to previously published results [13].

Avelumab is a fully human IgG1 mAb which, like atezolizumab and durvalumab, targets PD-L1. The phase Ib study (JAVELIN) trial enrolled 44 patients with mUC and prior platinum chemotherapy to receive avelumab 10 mg/kg every 2 weeks; the drug was tolerable with 6.8% of patients experiencing a grade 3/4 treatment related AE [14]. Avelumab also demonstrated clinical activity with an ORR of 18.8% (including a CR rate of 11.4%) with durable responses noted.

Pembrolizumab is a humanized IgG4k mAb targeting PD-1, which, like nivolumab, has been approved for use across a wide range of malignancies. Pembrolizumab is the only checkpoint inhibitor with full (as opposed to accelerated) USFDA approval for urothelial cancer based on the results of a large open-label randomized phase III trial (KEYNOTE 045) comparing pembrolizumab to investigator's choice chemotherapy in patients with mUC and prior platinum chemotherapy; this study revealed a statistically significant survival benefit for the patients who received