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Review – Urothelial Cancer

Systematic Review of Immune Checkpoint Inhibition in Urological Cancers

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Abstract

Context: In patients with advanced and metastatic urological cancers, clinical outcome may be improved by immune checkpoint inhibitors (ICIs).
Objective: To systematically review relevant literature on efficacy and safety of ICIs in patients with advanced and metastatic urothelial cell cancer (UCC), renal cell cancer (RCC), and prostate cancer.
Evidence acquisition: Relevant databases, including Medline, Embase, and the Cochrane Library, were searched up to March 16, 2017. A narrative review of randomized clinical trials (RCTs) was performed.
Evidence synthesis: Six RCTs were included for the systematic review. In platinum-pretreated UCC, efficacy of pembrolizumab was superior to chemotherapy, with longer median overall survival (OS; 10.3 vs 7.4 mo), a higher objective response rate (ORR; 21.1% vs 11.4%, $p = 0.001$), and a lower adverse event rate (60.9% vs 90.2%). Three RCTs assessed the safety and efficacy of nivolumab in advanced RCC. The median OS (25.0 vs 19.6 mo) and the ORR (25% vs 5%) were higher in patients treated with nivolumab compared with second-line everolimus. In all three studies, the safety profile of nivolumab was favorable. In patients with metastatic castration-resistant prostate cancer, two RCTs were identified, which did not show significant benefits for ipilimumab over placebo. In UCC and RCC, there was no conclusive association between programmed cell death receptor ligand 1 (PD-L1) expression in tumor tissue and clinical outcome during pembrolizumab and nivolumab treatment, respectively.
Conclusion: In metastatic UCC and RCC, pembrolizumab and nivolumab have superior efficacy and safety to second-line chemotherapy and everolimus, respectively. No beneficial effect of ipilimumab was observed in prostate cancer patients. PD-L1 expression status is currently not suitable as a predictive marker for treatment outcome.
Patient summary: Immune checkpoint inhibitors are able to reactivate the immune system against tumor cells. In second-line setting, pembrolizumab and nivolumab are safe and confer survival benefit in advanced urothelial cell and renal cell cancer, respectively.

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1. Introduction

Immune checkpoint inhibitors (ICIs) have shown efficacy in the treatment of a variety of solid tumors, including advanced urological cancers [1]. Historically, the treatment of urological malignancies included immune modulating agents. In high-risk non–muscle-invasive bladder cancer (NMIBC), adjuvant treatment with intravesical *Bacille Calmette Guérin* (BCG), a therapy that uses mycobacterial components to activate the immune system, provides a 32% risk reduction in recurrence compared with intravesical chemotherapy [2]. In addition, 10–20% of patients with metastatic renal cell cancer (mRCC) experience durable responses upon treatment with high-dose interleukin-2 [3]. The first commercially available autologous cell-based vaccination therapy, sipuleucel-T, was found to be effective in metastatic castration-resistant prostate cancer (mCRPC) [4]. Although immune modulating therapies have shown efficacy in these specific cases, systemic treatment of advanced and metastatic urological cancers thus far mainly comprises chemotherapy (for urothelial cell cancer [UCC] and prostate cancer [PC]), vascular endothelial growth factor (VEGF) pathway inhibitors (for mRCC), and androgen deprivation therapy (for PC).

Over the past 20 yr, standard first-line treatment for advanced and metastatic UCC has been cisplatin-based chemotherapy [5,6]. However, up to 50% of patients are unfit for cisplatin, mainly due to age-associated impaired renal function, cardiovascular comorbidities, and performance status [7]. Furthermore, no effective second-line treatment is available for patients with disease progression after first-line chemotherapy. Single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine) is commonly applied, but only 10% of patients experience a tumor response, and the median overall survival (OS) is around 7 mo [8].

In contrast with UCC, RCC is highly resistant to chemotherapy and, until the introduction of VEGF pathway inhibitors (eg, sunitinib and sorafenib) in 2005–2006, systemic treatment consisted of interferon-alpha and high-dose interleukin-2 [3]. Although VEGF pathway inhibitors, together with mammalian target of rapamycin (mTOR) inhibitors (eg, everolimus), have significantly improved the perspectives of mRCC patients [9], the median OS for mRCC patients remains only 12.5 mo after first-line targeted therapy [10].

In metastatic PC, androgen deprivation therapy is the backbone of treatment and frequently results in durable responses. Nevertheless, eventually all patients experience progression to mCRPC [11]. For the treatment of mCRPC, chemotherapy (docetaxel [12] and cabazitaxel [13]), second-generation antiandrogens such as abiraterone [14] and enzalutamide [15], and radionuclides such as radium-223 [16] have been approved. These agents have improved the survival in mCRPC patients; however, the median OS seems to plateau at about 3 yr [14,15].

The current lack of efficacious treatment options for advanced UCC, mRCC, and mCRPC underscores the clinical need for new well-tolerated treatment modalities that improve the outcome of patients with urological cancers. ICIs may expand the treatment armamentarium for patients with urological malignancies. Currently available ICIs include monoclonal antibodies that block the function of inhibitory receptors on T cells, resulting in a release of T-cell inhibition. Some tumors manage to escape immune surveillance by expressing the programmed cell death receptor ligand 1 (PD-L1) activating the inhibitory receptors on T cells and thereby preventing clearance by the immune system [17]. Interference with this receptor–ligand interaction by ICIs reinvigorates the T-cell–mediated antitumor immune response [18,19]. Thus far, blocking antibodies against programmed cell death 1 (PD-1; eg, nivolumab and pembrolizumab), PD-L1 (eg, atezolizumab), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; eg, ipilimumab) have been introduced in the clinic (Fig. 1).

The first hint of antitumor activity of ICIs in urological cancers came from phase I clinical trials, reporting durable responses in metastatic UCC and RCC [19,20]. Since then, several pivotal clinical trials evaluating the efficacy of ICIs in urological cancers have been initiated. In this systematic review, we analyzed the efficacy and safety of ICIs in patients with advanced urological cancers, including UCC, RCC, and PC.

2. Evidence acquisition

2.1. Search strategy

Up to March 16, 2017, an electronic search of the Medline, Embase, and Cochrane databases, and relevant websites (Web of Science and Google Scholar) was performed by an expert librarian. The search was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 2) [21]. Search terms included the following: "urinary tract cancer, bladder cancer, kidney cancer, prostate cancer, immune checkpoint inhibitors, atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, tremelimumab, anti-PD1, anti-PD-L1, and anti-CTLA-4" (see Supplementary materials for details). The search was completed by manual screening of reference lists from included studies.

2.2. Inclusion criteria

The study population consisted of patients (>18 yr of age), diagnosed with advanced or metastatic UCC, RCC, or PC, who were treated with one of the ICIs targeting PD-1 (nivolumab and pembrolizumab), PD-L1 (atezolizumab, avelumab, and durvalumab), and CTLA-4 (ipilimumab and tremelimumab). The search was limited to studies executed in humans. No restrictions in publication date or language were imposed. During the systematic review process, only prospective, randomized, phase 1, 2, and 3 clinical trials were included, whereas nonrandomized clinical trials (non-RCTs), case reports, editorials, letters, review articles, and conference abstracts were excluded. If multiple analyses of the same clinical study were performed, the most recent or most relevant publication was selected. Primary outcome measures included OS, progression-free survival (PFS), and

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