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Review article

Emerging role of immunotherapy in urothelial carcinoma—Future directions and novel therapies

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Abstract

Tremendous advances in our understanding of the tumor immunology and molecular biology of urothelial carcinoma (UC) have led to the recent approval of immunotherapy as a novel option for patients with UC with advanced disease. Despite the promising data of novel immune checkpoint inhibitors, only a small subset of patients with UC achieves durable remissions. Because an optimal antitumor response requires coordination of multiple immune, tumor, and microenvironment effector cells, novel approaches targeting distinct mechanisms of action likely in combination are needed. In addition, discovery of reliable immune biomarkers, understanding of mechanisms of resistance, and novel clinical trial designs are warranted for maximum benefit of UC immunotherapy.

Keywords: Urothelial carcinoma; Immunotherapy; Combination immune therapy; Immune biomarker; Novel clinical trial design

1. Introduction

Urothelial carcinoma (UC) of the bladder is the most common malignancy of the urinary tract and the sixth most common cancer in the United States with over 76,000 new cases and 16,000 cancer-related deaths in 2016 [1]. Although the bladder is the most common site of disease, UC can also present in the renal pelvis, ureter, and urethra. The overall prognosis of UC remains poor owing to a high recurrence rate in early-stage disease and the lack of effective systemic treatment in advanced disease [2]. Fortunately, there have been tremendous advances in our understanding of the tumor immunology and molecular biology of UC in recent years. This has led to the recent approval of checkpoint inhibitor immunotherapy for patients with postplatinum metastatic UC representing the first new metastatic UC drug approval in over 20 years. Indeed, the development of novel immunotherapeutic agents has opened a new frontier for UC management. In addition to immune checkpoint inhibitors, multiple immunotherapy agents are in development with relevance to UC (Fig.). In this review, we will highlight the recent clinical data and future directions of novel UC immunotherapy targets (Fig.).

2. Immune checkpoint inhibition: PD-1/PD-L1

Among multiple immunotherapeutic approaches, immune checkpoint inhibition has demonstrated the most promising clinical results. With blockade of the inhibitory receptors, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death-1 (PD-1), and its ligand, PD-L1 has shown durable antitumor responses in both solid and hematologic malignancies. In UC, both tumor and tumor-infiltrating lymphocytes (TILs) express PD-L1 in various frequencies at all stages, and its expression is associated with higher tumor grade and stage, resistance to Bacillus Calmette-Guérin (BCG) therapy, and inferior survival [3–5].

Atezolizumab is a humanized IgG1 anti-PD-L1 monoclonal antibody (mAb), which inhibits the binding of PD-L1

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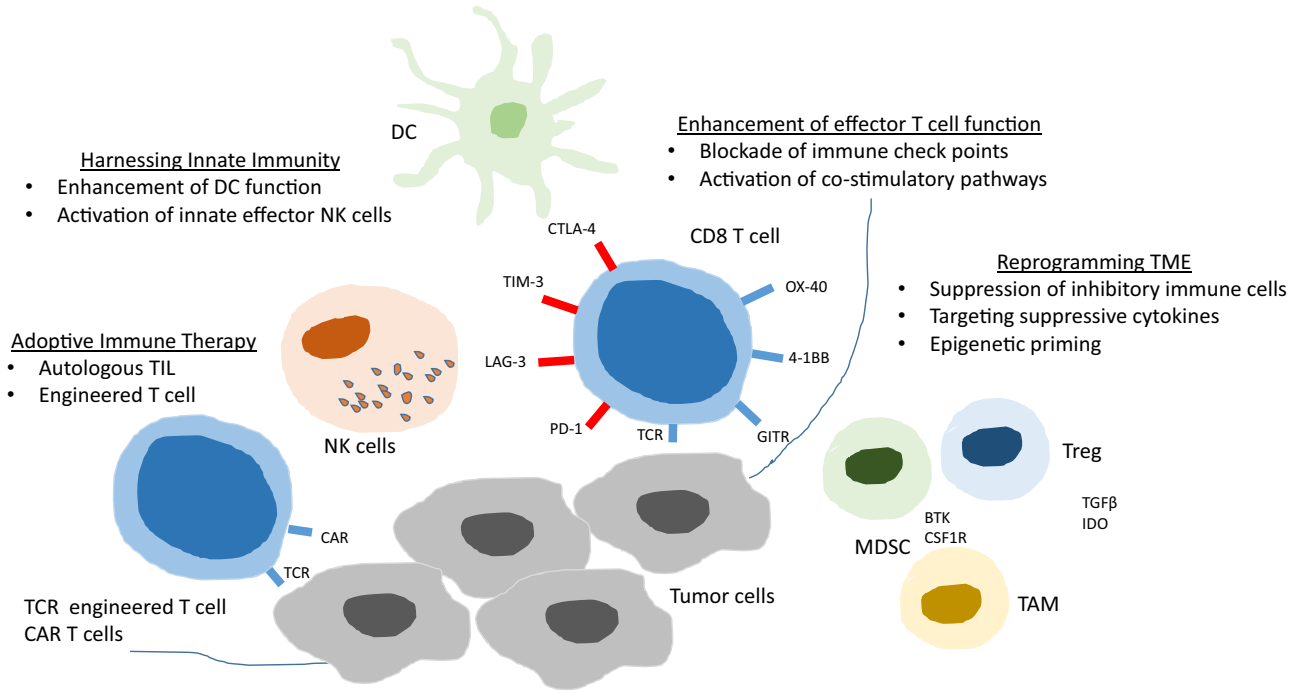

Fig. Selected immunotherapy targets in UC. (Color version of figure is available online.)

to PD-1 and B7.1. In a phase Ib study with an expanded UC cohort ($n = 92$), atezolizumab resulted in an overall response rate (ORR) of 50% with 9 complete responses (CR) in patients whose tumor-infiltrating immune cells (IC) have strong PD-L1 expression (immunohistochemistry [IHC] 2 and 3, defined as ≥5% and ≥10%, respectively) [6]. In a subsequent phase II study (IMvigor210) in patients with cisplatin-ineligible treatment-naïve (cohort 1) and postplatinum (cohort 2) advanced UC, atezolizumab showed an ORR of 15% in all comers and 27% in the IC PD-L1 IHC 2/3 subgroup with 12 CRs in 310 cohort 2 patients [7]. Median overall survival (mOS) in the all comers group was 7.9 months and 11.4 months in IC IHC 2/3 subgroup. Grade 3 to 4 treatment-related and immune-related adverse events (AEs) were reported in 16% and 5% of treated patients, respectively. The US Food and Drug Administration approved atezolizumab in May 2016 for the treatment of advanced UC following platinum-containing chemotherapy. In a cisplatin-ineligible subgroup (cohort 1) ($n = 119$), atezolizumab as a first-line therapy achieved an ORR of 24% with 7% CR rate with an estimated mOS of 14.8 months [8]. However, in this cohort of patients, the response rate was not significantly different between PD-L1 IHC subgroups. A randomized phase III trial of atezolizumab in comparison to standard chemotherapy in patients with postplatinum metastatic UC is ongoing (NCT02302807, Imvigor211).

Two other anti-PD-L1 mAbs, durvalumab and avelumab, also demonstrated similar promising antitumor efficacy and safety profiles. In a phase I/II study of durvalumab in patients with advanced UC, 16 of 42 evaluable patients for efficacy (38%) showed ORRs. PD-L1 expression was an independent predictor for response: the ORR in PD-L1 positive and negative patients were 54% and 7%, respectively [9]. In a phase I/Ib study of avelumab including 44 patients with advanced UC, 7 (16%) patients showed OR with 1 CR [10]. Grade 3 to 4 AE occurred in only 1 patient. Using a ≥5% cutoff, ORR was 40% (4/10) in patients with PD-L1 expressing tumor, whereas 9% (2/22) of patients with PD-L1-negative tumors also responded. A phase III trial evaluating the role of maintenance avelumab following the first-line platinum-containing chemotherapy in advanced UC is ongoing (NCT02603432).

Pembrolizumab is a humanized IgG4 mAb against PD-1 which is currently approved by the Food and Drug Administration for use in melanoma and non–small cell lung cancer treatment. In a phase Ib study of pembrolizumab in metastatic UC, 8 of 29 (28%) evaluable patients demonstrated ORs including 3 CRs [11]. According to analysis of PD-L1 expression, the ORR was 29% in 24 PD-L1-positive patients (>1% PD-L1 staining) and 0% among 4 PD-L1-negative patients. Grade 3 to 4 AEs occurred in 5 (15%) patients. Currently, pembrolizumab is being evaluated in postplatinum (NCT02256436), treatment-naive (NCT02335424), and as a maintenance following chemotherapy (NCT02500121) in advanced UC as well as high-risk local disease (NCT02625961). In a phase I/II study of nivolumab, a humanized IgG4 anti-PD-1 mAb, 24% of patients with advanced UC ($n = 78$) who were previously treated with platinum-based chemotherapy achieved ORs [12]. The ORR was not different based on PD-L1 expressions status; ORR in PD-L1 IHC < 1% and ≥1% cohort was 26.2% and 24.0%, respectively. Grade 3 to 4 AE rate was 20% with