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Review

Novel therapeutic targets in advanced urothelial carcinoma

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ABSTRACT

Bladder cancer remains one of the most common and lethal diseases that cause approximately 150,000 deaths per year worldwide. Over the past two decades, the options currently available to patients with invasive disease remained essentially unchanged and no effective drugs have been approved in that time. Cisplatin-based combination chemotherapy remains the standard of care for first-line systemic treatment of metastatic urothelial carcinoma. However, the major advances in understanding the genetic background of urothelial tumors open up a new therapeutic area. Here, we summarize the current state of development of targeted agents in urothelial cancer; with an emphasis on immune checkpoints inhibitors and FGFR targeted therapies that represent the most promising therapeutic approaches for invasive bladder cancer.

1. Introduction

With more than 380,000 new cases diagnosed each year and more than 150,000 deaths in 2013, bladder cancer is one of the most lethal malignancy worldwide (Siegel et al., 2013). Muscle-

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invasive bladder cancer (MIBC), representing 30% of bladder cancer at the initial diagnosis, constitutes a heterogeneous group of tumors with poor outcome (Hautmann et al., 2012). Approximately 25% of patients subjected to radical cystectomy present lymph node involvement at the time of surgery which is associated with decreased survival (Stein et al., 2001; Karl et al., 2009). As the roles for radical cystectomy and perioperative chemotherapy have become better defined in the management of localized disease, metastatic setting remains always almost incurable (Shah et al., 2011). For patients with advanced-stage disease or that relapse after radical surgery, the median survival rate is estimated to be only slightly more than 12 months (von der Maase et al., 2005). Since the past two decades, cisplatin-based combination chemotherapy remains the standard of care for first-line systemic treatment in metastatic urothelial carcinoma. So far, no substantial progress has been achieved in the treatment of MIBC. While cisplatin-based chemotherapy is only effective in 30–40% of patients and predictive biomarkers are not currently available (Shah et al., 2011), novel treatment approaches are urgently needed for this common and highly lethal disease.

New insights into the molecular biology of bladder carcinoma have highlighted several potential therapeutic targets (McConkey et al., 2014). As the whole genome sequencing is revolutionizing knowledge of cancer heterogeneity, the understanding of the genomic landscape of bladder cancer is ongoing (International Cancer Genome Consortium et al., 2010). Up to 60% of high-grade urothelial carcinomas harbor potentially actionable genetic alterations, particularly those involving the PI(3)K/AKT/mTOR, CDKN2A/CDK4/CCND1 and RTK/RAS pathways, including ERBB2 (Her-2), ERBB3 and FGFR3 (Cancer Genome Atlas Research Network, 2014; Iyer et al., 2013). The mutations identified in epigenetic pathways, including chromatin modifiers, also suggest new possibilities for bladder cancer treatment (Gui et al., 2011). Recently, three independent groups identified intrinsic subtypes of MIBC corresponding to two major basal and luminal subtypes with clinically distinct survival outcomes (Cancer Genome Atlas Research Network, 2014; Choi et al., 2014; Damrauer et al., 2014). Given their molecular similarities with breast cancer, these observations may have important implications for the future clinical development of targeted agents, and disease management with conventional chemotherapy (Rebouissou et al., 2014).

Arguably, targeting driver mutations has led to major improvements in several genetically defined solid tumors such as lung adenocarcinomas with EGFR mutations, EML4-ALK rearrangements, and BRAF-mutant melanomas (Mok et al., 2009; Kwak et al., 2010; Flaherty et al., 2010; Chapman et al., 2011). Indeed, the development of successful molecular-based therapies in bladder cancer remains challenging because of the high degree of biological diversity of urothelial carcinomas (Alexandrov et al., 2013). Thus, clinical trials design should to be founded on a more precise, biology-based approach classification of bladder cancer, including selected patients with targetable genomic alterations. Here, we summarize the current state of development of targeted agents directed against abnormal signaling pathway in urothelial cancer, with an emphasis on immune check-points inhibitors and FGFR targeted therapies that represent currently, the most promising new approaches for advanced urothelial carcinoma.

2. Immunotherapy

Since the last few years, immunotherapy has become an increasingly attractive therapeutic strategy in many solid tumors with the development of several agents including monoclonal antibodies, cancer vaccines and cytokine therapies (Mellman et al., 2011). Among the most notable therapeutic modalities to activating antitumor activity is the blockade of immune checkpoints that are able to enhance the immune response to tumors by restoring T lymphocytes activation (Pardoll, 2012). Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) antibodies were the first of this class to achieve a significant increase in survival for patients with metastatic melanoma (Hodi et al., 2010; Robert et al., 2011). Due to this recent proof-of-concept, the next generation T-cell immunomodulators are currently ongoing. In the context of clinical trials and cancer immunotherapy, one of the most actively studied is PD-1 (programmed cell death protein 1)/PD-L1 (PD-1 ligand) that is emerging as a promising target. PD-1 plays a key role as inhibitory receptor regulating immune response at multiple levels and by different mechanisms. Recently, the blockade of PD-1 and PD-1 ligand in metastatic bladder cancer has demonstrated spectacular improvement with an objective response rate and durable clinical benefit (Powles et al., 2014; Petrylak et al., 2015; Plimack et al., 2015).

2.1. Blocking PD-1/PD-L1 pathway

PD-1/PDL-1 pathway is probably one of the most important regulators of the immune response to a tumor (Robert et al., 2013). In contrast to CTLA-4 immunomodulation, the main role of PD-1 is to limit the activity of T cells in peripheral tissues during an inflammatory response to infection in order to limit autoimmunity (Chen et al., 2012). The PD-1 receptor is expressed on the surface of activated T cells. When PD-1 ligand binds to PD-1 receptor, an inhibitory signal is transmitted into the T cell reducing cytokine production and suppressing T-cell proliferation. Malignant cells are able to avoid immune destruction by diverting such immune checkpoint (Chen and Mellman, 2013). This translates into a major immune resistance mechanism within the tumor microenvironment (Dong et al., 2002). The clinical rationale for targeting the PD-1/PD-L1 pathways is based on increased PD-1 expression by TILs (tumor-infiltrating lymphocytes) and PD-1 ligand expression by tumor cells. This attractive approach consists in targeting the immunosuppression in tumor bed. Hence, PD-1 pathway blockade decreases the number and the activity of the regulatory T cells (Tregs), enhances the activity of effector T cells in tissues and tumor microenvironment, and therefore augments the intratumor immune response (Pardoll, 2012).

Recently, a phase I clinical trial (clinicaltrials.gov identifier: NCT1375842) evaluated an anti- PD-L1 monoclonal antibody Atezolizumab (MPDL3280A) in the second-line treatment of metastatic bladder carcinoma. Atezolizumab was well tolerated with manageable side-effects (Grade 3-4 immune-mediated adverse events rate was 5%). Forty-six of 87 (53%) patients tested positive for anti-PDL-1 were evaluable for efficacy at time of analysis with a median follow-up of 14 months. Impressively, the study indicates that 50% of PDL1 positive patients (IHC 2+ and IHC3+ assessed on immune cells) rapidly responded to immunotherapy with a median time to response of 62 days (1–10 months). Responders included patients with visceral metastases at baseline including nine patients with complete response. One-year overall survival rate was 57% in IC2/3 patients (Powles et al., 2014; Petrylak et al., 2015). The study is currently ongoing in a phase III clinical trial. Two other early-phase clinical trials are currently underway to develop anti-PD1 drug. A phase Ib study (clinicaltrials.gov identifier: NCT01848834) is evaluating monoclonal PD1 antibody, Pembrolizumab, in patients with advanced urothelial carcinoma. Pembrolizumab showed acceptable safety and tolerability and provides promising antitumor activity in patients with advanced urothelial cancer. Thirty-three patients were enrolled in this study. Overall response rate by central review was 28% (8/33) including 3 (10%) patients with complete responses. Median time to response was 9 weeks (7.7–55.9 weeks). One-year overall survival

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