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Immunotherapy advances in uro-genital malignancies

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ABSTRACT

Immunotherapy for the treatment of cancer has made significant progresses over the last 20 years. Multiple efforts have been attempted to restore immune-mediated tumor elimination, leading to the development of several targeted immunotherapies. Data from recent clinical trials suggest that these agents might improve the prognosis of patients with advanced genito-urinary (GU) malignancies. Nivolumab has been the first immune checkpoint-inhibitor approved for pre-treated patients with metastatic renal cell carcinoma. Pembrolizumab and atezolizumab have shown promising results in both phase I and II trials in urothelial carcinoma. Brentuximab vedotin has demonstrated early signals of clinical activity and immunomodulatory effects in highly pre-treated patients with testicular germ cell tumors.

In this review, we have summarized the major clinical achievements of immunotherapy in GU cancers, focusing on immune checkpoint blockade as well as the new immunomodulatory monoclonal antibodies (mAbs) under clinical evaluation for these malignancies.

1. Immune modulatory treatments in urinary tract malignancies

The increasing understanding of the molecular mechanisms that control the activation of adaptive immune responses and the

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accumulating evidence that interfering with these pathways can efficiently redirect the immune system against cancer, are now underscoring the power and versatility of immunotherapy to treat malignancies.

From the concept of cancer immunosurveillance, initially postulated by Ehrlich and theorized by Foley (1953) and Burnet (1957) we have become aware that the clinically detectable cancers are the results of a complex process; in this process the immune system plays an active role (Hanahan and Weinberg, 2011), by selecting the most immune silent/evasive tumor clones, which can proliferate due to the high genomic instability of cancer cells (Dunn et al., 2004). In the last 50 years, several efforts have been attempted to reestablish the conditions at the basis of immune-mediated tumor elimination in patients with clinically evident disease. Cancer vaccines, cytokines to sustain immune activation and effector functions, adoptive T-cell therapy, and passive immunotherapy with tumor-specific mAbs have been some of the strategies used. However, besides the clinical efficacy of antitumor mAbs, such as anti-CD20 rituximab and anti-Her2 trastuzumab, which partially depends on immune-mediated destruction of malignant cells, these approaches failed to demonstrate the possibility to consistently reactivate the immune system against cancer.

As for infectious pathogens, recognition of tumor cells by the immune system involves engulfment, processing and display of tumor proteins by antigen presenting cells (APCs), such as dendritic cells (DCs), to specific T lymphocytes in secondary lymphoid organs. Activation of naïve T cells requires concurrent engagement of T-cell receptors by cognate peptides in the context of major histocompatibility complex (MHC) and co-stimulatory molecules expressed on mature APCs. Since APCs mature and express co-stimulatory molecules only upon sensing "danger" signals released from dying infected/tumor cells (Kono and Rock, 2008), this 2-signal system is meant to ensure specific activation of potentially pathogenic killer T cells only against actual "pathogens". Time and space-dependent expression of co-stimulatory and co-inhibitory receptors on T cells and the respective ligands on APCs, controls and regulates induction, execution and termination of adaptive immune responses. In particular, induction of CD80 and CD86 on mature APCs is required to properly co-stimulate antigen specific T cells through CD28 (Chen and Flies, 2013). Activated T cells promptly up-regulate the alternative co-inhibitory receptor for the same ligands CTLA-4 (cytotoxic T lymphocyte antigen 4), which dampens T-cell functions and constitutes one of the major checkpoints of immune responses (Krummel and Allison, 1995). In case of persistent antigenic stimulation, as can occur in cancer, another key immune checkpoint is induced: PD-1 (programmed cell death-1), which potently inhibits T-cell effector function and expansion upon engagement by its ligands PD-L1 (programmed death ligand-1) and PD-L2 (programmed death ligand-2) expressed on both myeloid cells and tumor cells (Ishida et al., 1992). Up-regulation of PD-L1 in normal tissues is a mechanism that normally protects against T-cell cytotoxicity in case of inflammatory reactions. Tumor cells exploit this function to block T-cell infiltration and activity through the engagement of PD-1 on activated T cells (Topalian et al., 2012a; Tumeh et al., 2014). Blocking this interaction through specific mAbs has shown promising results towards the restoration of T-cell effector functions and tumor killing. Additional immunomodulatory T-cell co-receptors have been discovered highlighting the complexity of the signaling network that normally fine-tunes T-cell activation, differentiation, survival, effector functions and that can be altered in the presence of cancer. They can be divided into two major categories of receptors:

1. The immunoglobulin superfamily (IgSF), including the co-stimulatory receptors CD28 and ICOS (inducible T-cell costimulator), and the co-inhibitory receptors CTLA-4, PD-1, LAG3 (lymphocyte activation gene 3 protein), TIM3 (T-cell membrane protein 3) and BTLA (B and T lymphocyte attenuator);
2. The tumor necrosis factor receptor superfamily (TNFRSF), including co-stimulatory members, such as GITR (glucocorticoid-induced TNFR-related protein), OX40, CD30, CD40, CD27, and 4-1BB (Chen and Flies, 2013).

Hampered co-stimulation has emerged as one of the major limitations to the clinical success of anti-tumor immunotherapy (Ochsenbein et al., 1999). Tumor-antigen specific T cells have been identified in cancer patients, but they are usually anergic, exhausted or actively inhibited by immunosuppressive cells. Interestingly, all these circumstances are associated with an unbalanced expression of co-inhibitory receptors and ligands. T cells become anergic when they encounter cognate-antigen presenting DCs lacking co-stimulatory molecules and/or expressing inhibitory ligands (Hawiger et al., 2001; Probst et al., 2003). Chronic T-cell exposure to tumor antigens promotes overexpression of co-inhibitory receptors, in particular PD-1 and LAG-3, which prevent further activation of the TCR signaling pathway and maintain dysfunctional T cells (Yi et al., 2010). Immunosuppressive cells, which block T-cell activation and functions, typically expand in the tumor microenvironment and are characterized by high expression levels of co-inhibitory receptors and/or ligands (Lindau et al., 2013).

Recognition of these common aspects in tumor-bearing hosts' lymphocytes led to the hypothesis that interfering with co-inhibitory pathways could be a successful immunotherapeutic strategy to overcome immune tolerance and induce long-lasting antitumor effects. Thanks to the development of CTLA-4 and PD-1 blocking mAbs, this hypothesis was demonstrated first in animal models and then in clinical studies (Topalian et al., 2012a; Hodi et al., 2010; Brahmer et al., 2012a; Hamid et al., 2013; Wolchok et al., 2013; Robert et al., 2014; Larkin et al., 2015), with the Food and Drug Administration (FDA) approval of these agents for the treatment of metastatic melanoma in 2011 and 2013 respectively. Anti-CTLA-4 ipilimumab and anti-PD-1 nivolumab and pembrolizumab showed for the first time the possibility to increase survival of advanced metastatic melanoma patients. Importantly, the FDA extended the approval of nivolumab to advanced non-small cell lung cancer and renal cell carcinoma (RCC) based on the ability of the drug to prolong survival also in these patients. Besides the remarkable clinical impact of these results, they formally demonstrate that this immunotherapeutic approach can significantly benefit cancer patients across a wide range of malignancies.

Urologic cancers are among the tumor categories where immunotherapy has been more extensively studied. Intravesical administration of the weakened Calmette-Guérin Bacillus (CGB) was the first FDA-approved immunotherapy in patients with non–muscle-invasive urothelial bladder cancer (Morales, 1980). Immunostimulatory cytokines (interleukin-2 and interferon-alpha) have been used for more than a decade to treat kidney cancer (McDermott, 2007). Prostate cancer was the first indication for which an immunotherapy (sipuleucel-T, Provenge®) was granted the FDA approval in 2010, upon the demonstration of survival improvement and death risk reduction in a subset of vaccinated hormone-refractory patients (Kantoff et al., 2010a). However, efficacy of these immunotherapies is limited to a small number of patients. Specifically, the role of CGB against bladder cancer recurrence is not clearly defined, selection of kidney cancer patients for high-dose cytokines has not been ameliorated thus preventing their widespread administration due to the possibility of serious side effects, and the autologous DC-based anti-prostate cancer vaccine sipuleucel-T carries the intrinsic drawback to require patient-specific preparations, besides skepticism regarding its actual efficacy.