Critical Reviews in Oncology/Hematology 113 (2017) 292–303

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review article

A comprehensive review of immunotherapies in prostate cancer

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Contents

ARTICLE INFO

Article history:
Received 13 January 2017
Received in revised form 28 February 2017
Accepted 28 February 2017

Keywords:
Prostate cancer
Metastatic
Castration-resistant
Immunotherapy
Immune checkpoint inhibitor

ABSTRACT

Prostate cancer is the second most common malignant neoplasm in men worldwide and the fifth cause of cancer-related death. Although multiple new agents have been approved for metastatic castration resistant prostate cancer over the last decade, it is still an incurable disease. New strategies to improve cancer control are needed and agents targeting the immune system have shown encouraging results in many tumor types. Despite being attractive for immunotherapies due to the expression of various tumor associated antigens, the microenvironment in prostate cancer is relatively immunosuppressive and may be responsible for the failures of various agents targeting the immune system in this disease. To date, sipuleucel-T is the only immunotherapy that has shown significant clinical efficacy in this setting, although the high cost and potential trial flaws have precluded its widespread incorporation into clinical practice. Issues with patient selection and trial design may have contributed to the multiple failures of

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http://dx.doi.org/10.1016/j.critrevonc.2017.02.026

Vaccines
Oncolytic viruses

immunotherapy in prostate cancer and provides an opportunity to tailor future studies to evaluate these agents more accurately. We have reviewed all the completed immune therapy trials in prostate cancer and highlight important considerations for the next generation of clinical trials.

1. Introduction

Prostate cancer (pCa) is the second most common cancer in men, with an estimated 1.1 million patients diagnosed worldwide yearly (Siegel et al., 2016). Furthermore it is the fifth leading cause of cancer mortality in men accounting for 6.6% of total male deaths (Siegel et al., 2016). The majority of new cases are localized or locally advanced, with 20% to 30% of these patients relapsing after curative intent therapy (Howlader et al., 2016; Abdollah et al., 2012). Less than 5% of patients present with de novo metastatic pCa (Howlader et al., 2016). Eight clinical states of pCa have been described and metastatic disease is divided into hormone sensitive (HSPC) and castrate refractory (CRPC) settings (Scher et al., 2015).

For men with metastatic CRPC (mCRPC), the median overall survival (OS) in recent phase 3 studies has ranged from 12.2 to 34.7 months (Kantoff et al., 2010a; Berthold et al., 2008; De Bono et al., 2010; Parker et al., 2013; Beer et al., 2014; Ryan et al., 2015). Table 1 outlines the various treatment options for mCRPC with hormonal, chemotherapy, radiopharmaceutical and immunotherapy agents. These therapies have demonstrated significant improvements in overall survival but ultimately metastatic pCa currently remains incurable.

Targeting the immune system represents an appealing option for the development of anticancer treatment. There are several classes of immune therapies such as immune checkpoint inhibitors, co-stimulatory antibodies, vaccines, adoptive cell transfer, tumor infiltrating lymphocytes, oncolytic viruses and cytokines. The cancer vaccine sipuleucel-T has been approved for use in mCRPC by the US Food and Drug Administration (FDA) and recent early phase trials of programmed cell death protein-1 (PD-1) inhibitors have reported promising activity, which support the enthusiasm to develop immune therapies in pCa (Kantoff et al., 2010a; Hansen et al., 2016; Graff et al., 2016). Notwithstanding there have been several notable immunotherapy failures in pCa and correlative studies have demonstrated that the prostate tumor microenvironment is predisposed toward immunosuppression (Zhang et al., 2014; Pasero et al., 2016; Shafer-Weaver et al., 2009). Here we review immunotherapies that have been tested in pCa, highlighting the spectrum of new agents and combinations. We also examine potential biomarkers and aspects of clinical trial design for immunotherapies.

2. Cancer and the immune system

Tumors occur in the setting of a dysregulated immune system (Hanahan and Weinberg, 2011). The immune system provides several protective mechanisms such as removing viruses that can induce tumor formation, suppressing tumorigenic inflammatory reactions and eliminating tumor cells. Cancer initiation occurs following oncogenic cellular transformation and failure of intrinsic tumor suppressor processes. Beyond these events the cancer immunoediting concept describes 3 phases that regulate the immune system-tumor interaction (Dunn et al., 2004).

The elimination phase involves innate and adaptive immunity removing tumor cells. Those tumor cells that remain enter a state of quiescence and exist in equilibrium with adaptive immune cells. Over time under the ongoing pressure applied by the immune system, tumor cells escape the equilibrium to proliferate unchecked without regulation by immune cells (Smyth et al., 2006). Tables 2 and 3 summarize the described concepts.

The anti-tumor immune response is cyclical, starting with recognition of tumor neo-antigens by specialized antigen-presenting cells (APCs). Subsequently, APCs present antigen to effector T cells and when this occurs in the setting of an appropriate secondary signal, it leads to activation of T cells that then migrate to the tumor microenvironment where they remove cancer cells expressing those antigens (Chen and Mellman, 2013). However, an intricate network of stimulatory and inhibitory signals regulates this response that will ultimately produce ongoing immune cell activation or suppression within the resultant infiltrate and has been associated with patient prognosis (Clemente et al., 1996; Predina et al., 2013; Pages et al., 2005; Schreiber et al., 2011; Fridman et al., 2012). The type, density and spatial distribution of infiltrating lymphocytes are strongly correlated with survival (Naito et al., 1998; Sato et al., 2005; van Houdt et al., 2008), which supports the development of immune therapies to enhance antitumor immune responses (Yuan et al., 2010). Fig. 1 summarizes the immunoediting process and the mechanisms of action of immune agents tested in pCa.

3. Prostate cancer microenvironment

Observations about the pCa microenvironment suggest that it is predominantly immunosuppressive. The findings that support this include a low cytolytic activity of NK cells within prostate tumor bed (Pasero et al., 2016), higher secretion of TGF-beta by prostate tissue, which inhibits NK cell and lymphocyte function (Flavell et al., 2010), and the recruitment and accumulation of T regulatory cells (Tregs) and T_H17 lymphocytes that down-regulate antitumor immunity (Miller et al., 2006; Sfanos et al., 2008).

Levels of TGF-beta in prostate tissue are associated with high gleason scores, higher pathologic tumor stage and increased likelihood of post-operative residual tumors in localized pCa (Reis et al., 2011). Furthermore in the metastatic setting, TGF-beta concentrations are correlated with tumor burden (Drake, 2010).

The prostate immune microenvironment is dynamic, changing over time, clinical states and with treatment exposure. The latter is characterized by a series of phenotypic alterations leading to immunomodulation (Ardiani et al., 2014) such as increased tumor infiltrating lymphocytes (TIL) in the prostate bed following androgen deprivation therapy (ADT) (Thoma, 2016; Gannon et al., 2009) or sensitization of tumor cells to T-cell mediated lysis following enzalutamide and abiraterone exposure (Ardiani et al., 2014), and higher levels of PD-1 ligand (PD-L1) and PD-L2 expression on enzalutamide resistant prostate cancer cells (Bishop et al., 2015).

4. Immunotherapy in prostate cancer

Immunotherapy is focused on agents developed to harness the host's immune system to target and destroy malignant cells. It may involve various immune mechanisms, such as stimulating recognition and elimination of non-self antigens, augmenting or propagating the antigen presentation process, priming T cells,