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Professional paper

CHALLENGES IN MANIPULATING IMMUNE SYSTEM TO TREAT PROSTATE CANCER

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SUMMARY – First cancer vaccine that was approved for routine therapy was sipuleucel-T for treatment of patients with metastatic castration resistant prostate cancer. However, other immunotherapy drugs evaluated in prostate cancer, particularly immune checkpoint inhibitors, have failed to show therapeutic effect. There are several potential explanations for lack of response of prostate cancer to these drugs. These explanations, which are related to specific genetic (e.g. low mutational burden) and immunological (e.g. immunosuppressive tumor immune microenvironment) background of prostate cancer are discussed in this review. Also, new therapeutic strategies to overcome prostate cancer immunotherapy resistance and to select subgroups of patients that could benefit from immunotherapy are outlined.

Key words: *Prostate Cancer; Immunotherapy; Cancer Vaccines; Immune Checkpoint Inhibitors; Tumor Immune Evasion*

Introduction

Prostate cancer is second most common cancer in men, with an estimated 1,100,000 new cases and 307,000 deaths in 2012 worldwide (1). Patients with localized prostate cancer are successfully treated by surgery and radiotherapy. For patients with metastatic prostate cancer, androgen deprivation therapy is the standard treatment. However, most of these patients progress into metastatic castration resistant prostate cancer (mCRPC) and eventually die after progression (2).

Different therapeutic approaches are studied for patients with mCRPC with special interest in immunotherapy. Cancer immunotherapy is any of various therapeutic approaches (cancer vaccines, immune checkpoint inhibitors (ICI), chimeric antigen receptor (CAR) T-cells, etc.) that aim at patient's own immune system to make it more efficient at killing cancer cells. Only approved therapeutic cancer vaccine, sipuleucel-T, was approved for patients with asymptomatic or minimally symptomatic mCRPC (3). ICI are type of immunotherapy drugs that are currently widely used in different types of cancer (melanoma, lung cancer, bladder cancer, etc.) with significant therapeutic effect. However, clinical studies in prostate cancer have not shown significant therapeutic effect of ICI (4,5). To understand why ICI have failed so far as drugs for prostate cancer and to develop more efficient immunotherapies we need to better understand complex relations between prostate cancer and immune system. Recent discoveries in that field will be discussed later in this review.

Understanding how immune system influences prostate cancer and vice versa could help us improve management of prostate cancer patients in many different ways. For example, it was shown that immune cells can be responsible for one mechanism of developing prostate cancer castration resistance (6). Studies also indicate that immunological mechanisms may be

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responsible for beneficial effects of exercise that was shown to improve quality of life in patients with prostate cancer (7).

Sipuleucel-T and other cancer vaccines

Sipuleucel-T was the first cancer vaccine that was approved for routine treatment of cancer patients. After promising phase I/II trial results, sipuleucel-T was analyzed in three large phase III trials (8-10). First two of these trials had progression-free survival as primary endpoint that was not reached but both studies have shown better overall survival for patients treated with sipuleucel-T compared to placebo control (8,9). Pooled data from these two trials have shown median overall survival of 23.2 months in sipuleucel-T group versus 18.9 months in placebo control group (hazard ratio=0.67 (95% CI 0.49-0.91), p=0.011) (8,9). In a pivotal phase III study (IMPACT trial) on 512 patients with mCRPC primary goal of prolonged overall survival was met (median 25.8 versus 21.7 months, hazard ratio=0.78 (95% CI 0.61-0.98), p=0.03) (10). In all three clinical trials sipuleucel-T was well tolerated with most side effects being grade I or II and resolving within two days (11). Based on results of IMPACT trial, sipuleucel-T was approved in 2010 by the U.S. Food and Drug Administration for treatment of patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer. Sipuleucel-T is also studied in other categories of prostate cancer patients. There is ongoing ProVent phase III study testing effectiveness of sipuleucel-T in decreasing histologic progression in patients with low-grade prostate cancer. Sipuleucel-T is not widely accepted with recent analysis showing that only 10% of eligible mCRPC patients in the USA were treated with sipuleucel-T (12). Reasons for low acceptance of sipuleucel-T could be its high price and complexity of its application compared to other drugs for mCRPC like abiraterone acetate and enzalutamide.

Sipuleucel-T is an individualized cancer vaccine prepared from patient's peripheral blood mononuclear cells. These cells are harvested from patient's blood and incubated *ex vivo* with recombinant antigen PA2024 that consists of prostate cancer antigen prostatic acid phosphatase (PAP) fused to human granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF facilitates activation and maturation of dendritic cells that are returned to the patient. These dendritic cells are supposed to activate patient's adaptive immune response that will target prostate cancer cells that express PAP. Immunological effects and mechanisms of sipuleucel-T were studied to better understand its complex activity but also to potentially find predictive biomarkers that would help select patients most likely to benefit from sipuleucel-T treatment. It was shown that sipuleucel-T induces infiltration of activate T cells into prostate cancer tissue (13). Sipuleucel-T also induces systemic T-cell response specific to PA2024 antigen that is related to its therapeutic effect on patients' survival (14). In addition to cellular immunity, sipuleucel-T was shown to elicit adaptive humoral immune response with IgG antibodies specific to PAP and PA2014 antigens, but also to other non-target prostate cancer antigens like PSA (15,16). Antibody response to non-target antigens PSA and LGALS3 was associated with improved survival in prostate cancer patients treated with sipuleucel-T (16). Such antibody response to non-target antigens can be explained by antigen spread mechanism that could be responsible for part of therapeutic effect of sipuleucel-T and other similar immunotherapies (17).

There are other cancer vaccines that have been studied in patients with prostate cancer but so far without results of clinical trials that would justify their use in routine practice (18). Cancer vaccine PROSTVAC-V/F based on recombinant vaccinia and fowlpox viral vectors genetically engineered to express prostate specific antigen (PSA) has shown very promising results in phase II studies (19). However, large phase III clinical study on 1297 patients failed to show Prostvac-V/F effect on patients' survival (20).

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICI) are antibodies that target inhibitory receptors on cytotoxic T cells (CTLA-4 and PD-1) or ligands for these receptors on other cells (PD-L1). In that way they block activation of these inhibitory receptors and in effect augment activation of T cells with expected enhanced anti-cancer immune response. With proven significant therapeutic efficiency in different types of cancer these drugs have changed the landscape of cancer therapy in the last decade.

Unfortunately, unlike in many other cancer types including renal cell carcinoma and urothelial carcinoma, ICI have shown very limited effect in prostate cancer. Ipilimumab, anti-CTLA-4 antibody failed to show any improvement in overall survival in two phase III studies on patients with mCRPC (21,22). The largest study of anti-PD-1 antibody pembrolizumab in patients with mCRPC with published preliminary data, KEYNOTE-199 showed objective response rate of 5% in 133 patients with measurable PD-L1-positive disease and 3% in 66 patients with measurable PD-L1-negative disease (23).

Immunological background of prostate cancer immunotherapy resistance and ways to overcome it

Current understanding of local and systemic relations between immune system and cancer in the context of immunotherapy offers several explanations for failure of ICI in prostate cancer and potential strategies to improve immunotherapy effects in patients with prostate cancer and select subgroups of patients that might respond to ICI.

Partial explanation for lack of response to ICI in prostate cancer can be low tumor mutation burden (number of mutations in cancer cells) in prostate cancer compared to some other types of cancer that have good response to ICI (e.g. melanoma and lung cancer) (24). Higher tumor mutation burden was associated with better response to ICI in different types of cancer including prostate cancer (25,26). Higher tumor mutation burden relates to higher number of neoantigens expressed by cancer cells that can be recognized by cytotoxic T cells, principal type of cells activated by ICI. Cancers with deficient mismatch repair (dMMR), characterized with high level of microsatellite instability (MSI-H) usually have more mutations compared to same types of cancer that are not deficient in MMR. Based on a study in different types of dMMR/MSI-H cancers that has shown high objective response rate with ICI, pembrolizumab was approved in 2017 by FDA for second-line treatment of dMMR/MSI-H advanced cancers of any histologic type (27). Prevalence of dMMR/MSI-H in prostate cancer is 3-8%, and these patients might be good candidates for ICI (28,29). Retrospective analysis of eleven mCRPC patients with dMMR/MSI-H cancer treated with ICI has shown >50% decline in PSA levels in six patients and radiographic response in four patients (28). Genetic aberrations in prostate cancer in other genes related to DNA damage response (eg. *BRCA2*) might be associated with favorable response to ICI (30). It was shown that prostate cancer with loss of *CDK12* gene found in 7% of mCRPC represents a distinct subgroup of prostate cancer with increased neoantigen load and potential response to ICI (31).

Another potential mechanism of escaping immune response by prostate cancer is downregulation of MHCI expression resulting with impaired antigen presentation to cytotoxic T cells. Potential marker of response to anti-PD1/PD-L1 ICI is expression of PD-L1 on cancer cells. However, response to ICI in prostate cancer does not appear to be related to PD-L1 expression (23,30).

It was shown that analysis of tumor-infiltrating lymphocytes, but also more complex analysis of tumor immune microenvironment might predict cancer prognosis, response to immunotherapy and response to other modalities of cancer treatment (32,33). Based on presence and location of tumor-infiltrating lymphocytes, tumors are classified as immunologically "hot" (T cell inflamed) or "cold" (non-T cell inflamed). Immunologically "hot" tumors are more likely to respond to immunotherapy. Although T cell infiltrates can be found in prostate cancer, it is possible that these T cells are dysfunctional contributing to immunosuppressive prostate cancer immune microenvironment (33). Immunosuppressive prostate cancer microenvironment might also be enhanced by the presence of immunosuppressive immune cells like regulatory T cells and myeloid-derived suppressive cells (MDSC) that were confirmed in prostate cancer tissues (34-36).

One strategy to overcome resistance and improve immunotherapy outcomes in patients with prostate cancer is to combine different immunotherapies (dual ICI, ICI + cancer vaccines) or immunotherapies with other types of therapy (ICI + PARP inhibitors, ICI + chemotherapy, ICI + radiotherapy, ICI + androgen-deprivation therapy). These combinations are currently studied in many ongoing clinical trials (37-39). Rationale for these combinations is based on current understanding of immune mechanisms of different therapeutic approaches: potential of cancer vaccines to induce immune infiltration to tumor microenvironment and enhance effects of ICI, known immunomodula-

tory effects of chemotherapy and radiotherapy, etc. (38,40).

Conclusion

Despite being the first cancer with approved cancer vaccine therapy, results of immunotherapy in prostate cancer so far have been disappointing compared to some other types of cancer. Several new therapeutic strategies to overcome prostate cancer immunotherapy resistance and to select subgroups of patients that could benefit from immunotherapy emerged from new insights into biology of prostate cancer and are explored in ongoing clinical studies. However, real clinically important breakthrough in prostate cancer immunotherapy might come from future innovative approaches that will be based on deeper understanding of complex interplay between prostate cancer and immunity, interplay that we are only starting to fully comprehend.

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Sažetak

IZAZOVI MANIPULIRANJA IMUNOLOŠKIM SUSTAVOM U SVRHU LIJEČENJA RAKA PROSTATE

I. Šamija i *A. Fröbe*

Prva vakcina za rak koja je odobrena za rutinsko liječenje bio je sipuleucel-T za liječenje bolesnika s metastatskim kastracijski rezistentnim rakom prostate. Međutim, drugi imunoterapijski lijekovi koji su bili istraživani u bolesnika s rakom prostate, posebno inhibitori imunološke kontrolne točke, nisu pokazali terapijski učinak. Nekoliko je mogućih objašnjenja za nedostatak terapijskog odgovora na ove lijekove kod raka prostate. Ta objašnjenja koja su vezana uz specifična genetička (npr. nisko mutacijsko opterećenje) i imunološka (npr. imunosupresivni tumorski imunološki mikrookoliš) obilježja raka prostate opisana su u ovom preglednom radu. Također, prikazane su nove terapijske strategije s ciljem prevladavanja otpornosti raka prostate na imunoterapiju i za odabir podskupina bolesnika u kojih se može očekivati korist od imunoterapije.

Ključne riječi: *rak prostate; imunoterapija; vakcine za rak; inhibitori imunološke kontrolne točke; izmicanje tumora imunološkom nadzoru*