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PROSTATE CANCER IMMUNOTHERAPY

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Summary

Prostate cancer is one of the most commonly diagnosed cancers in men and also one of the leading causes of their cancer-related deaths. Despite recent advances in the treatment of metastatic castration resistant prostate cancer, agents providing durable disease control and long-term survival are still needed. Therefore, various anti-cancer immunotherapy approaches are being explored in prostate cancer patients. This review provides a short overview of the various approaches. However, apart from the vaccine sipuleucel-T which has received approval from the US Food and Drug Administration (FDA), the majority of other approaches have still not reached phase 3 clinical trials.

KEY WORDS**:** *prostate cancer, immunotherapy, vaccines*

IMUNOTERAPIJA KARCINOMA PROSTATE

Sažetak

Rak prostate po incidenciji i mortalitetu spada među najčešće tumore u muškaraca. Usprkos nedavnim postignućima u liječenju hormonski rezistentnog raka prostate, i dalje postoji potreba istraživanja i pronalaženja lijekova koji mogu omogućiti kvalitetnu dugotrajnu remisiju metastatske bolesti ili izlječenje. Posljedično, istraživanja uključuju i razne imunoterapijske pristupe. U prikazanom radu dan je kratak pregled imunoterapijskih pristupa. Međutim, osim vakcine sipuleucel-T, koja je adobrena od američke agencije za hranu i lijekove, većina drugih imunoterapijskih pristupa nije ušla u treću fazu kliničkog ispitivanja.

KLJUČNE RIJEČI: *rak prostate, imunoterapija, vakcine*

INTRODUCTION

Prostate cancer is both one of the most common cancers in men and a very frequent cause of cancer mortality among them (1-3). The treatment of prostate cancer patients involves a multidisciplinary approach which traditionally includes surgery, radiotherapy, hormonal or androgen deprivation therapy and chemotherapy. The treatment strategy depends on the patient's age, his general condition (performance status) and organ systems functional status, prostate cancer pathohistological characteristics, disease extent and distribution in the body (tumor stage), availability of particular treatment possibilities and the patient's decision on and choice of the possible treatment options. Radical prostatectomy or radical radiotherapy (+/- androgen deprivation therapy) are the main therapeutic option for patients with localized prostate cancer. For patients having metastatic prostate cancer, the first therapeutic option of active oncological treatment is androgen deprivation therapy (medical or surgical castration). When patients develop the so-called castration-resistant prostate cancer, active systemic oncological treatment options can include chemotherapy

(usually starting with docetaxel), additional hormonal therapy based on androgen synthesis inhibitor abiraterone, antiandrogen drug enzalutamide or alpha-emitting radium-223 (4-6). Moreover, there is also the immunotherapeutic option, based on the only US Food and Drug Administration (FDA) approved tumor vaccine sipuleucel-T.

Sipuleucel-T vaccine

Sipuleucel-T vaccine was FDA approved in 2010. It is prepared individually from the patient's autologous peripheral mononuclear cells. Vaccine preparations start with their extraction by a leukapheresis procedure. After extraction, these cells are incubated *in vitro* with a recombinant fusion protein (PAP-GM-CSF) consisting of the antigen prostatic acid phosphatase (PAP), which is present in 95% of prostate cancer cells, and of granulocyte-macrophage colony stimulating factor (GM-CSF) that helps mononuclear cells to mature to dendritic cells which are professional antigen-presenting cells. These activated cells are thereafter reinfused into the patient. A complete sipuleucel-T treatment includes three courses at two-week intervals. Sipuleucel-T vaccine is indicated for patients having castration-resistant diseases, who are asymptomatic or minimaly symptomatic (in biochemical relapse), have no liver metastases, whose life expectancy exceeds 6 months, and whose ECOG performance status is 0 – 1. Sipuleucel-T has been shown in a phase 3 clinical trial to extend mean survival from 21.7 months in the control arm to 25.8 months in the treatment arm, which constitutes a 22% reduction in mortality risk. The cells that have been reinfused into patients in the control arm have not been *in vitro* incubated with the recombinant protein PAP-GM-CSF. Common sipuleucel-T complications include chills, pyrexia and headache (5,7,8).

Other immunotherapeutic approaches

Prostate cancer patients can figuratively be said to have a cancer that is convenient for immunotherapeutic anti-cancer testings and treatments. The prostate as a body organ has relatively a lot of tissue specific molecules that can be considered as potential target antigens for anti-cancer immunotherapeutic treatments. By targeting prostate cell specific molecules, there is a lower chance, if an anti-cancer immune response can be evoked, of having as a side-effect cross-reactive autoimmune reactions against the cells in other tissues and organs. Moreover, the prostate as an organ can be considered as a non-vital (discarding) organ, which should consequently reduce concerns regarding the autoimmune destruction of normal prostate cells. In addition, as a reliable serum marker that is furthermore easily obtainable, PSA can be used for assessing the clinical response in treated patients. However, apart from the above mentioned sipuleucel-T, none of the other anti-prostate cancer immunotherapies have as yet proven to be of any promising clinical utility. An overview of prostate cancer clinical immunotherapeutical approaches can be obtained at https://clinicaltrials.gov (9). For example, these various approaches explore the intratumoral/intraprostate delivery of immune system activating cytokines and the administration of various vaccines. A vaccination clinical study on vaccinia/fowlpox virus-based vaccine encoding PSA (PSA-TRICOM) has reached the Phase 3 approval trial in patients with metastatic prostate cancer. More recent clinical approaches are also looking into the use of adoptive cell therapy using *ex vivo* expanded tumor-reactive T cells or T cells engineered to be specific for a particular tumor antigen by transfecting them *in vitro* with the so-called chimeric antigen receptors (CAR) that permit recognition of a cell-surface proteins using an antibody recognition domain fused to the T-cell receptor signaling domain. Another approach aimed at increasing the reactivity of T cells to tumor cells uses bispecific antibodies (BiTEs, bispecific T-cell engagers). These are a class of artificial bispecific monoclonal antibodies that are being investigated as anti-cancer drugs. They are structured as a binding domain of two antibodies, one specific for the T lymphocyte (eg. CD3) and the other specific for a desired membrane antigen on tumor cells, that are fused together. BiTEs form a link between T cells and tumor cells. This causes T cells to exert cytotoxic activity on tumor cells by producing cytotoxic proteins like perforin and granzymes, independently of the presence of MHC I or co-stimulatory molecules. These cytotoxic proteins enter tumor cells and initiate the tumor cell's apoptosis. As opposed to the CARs T cells, the advantage of the BiTEs, like that of any monoclonal antibodies, is that they are an off-the-shelf product and consequently a more easily and widely applicable treat-

ment option. Another class of monoclonal antibodies which, by being directed against the so-called inhibitory receptor molecules on T-lymphocytes (checkpoint molecules), block the generation of inhibitory signals within T lymphocytes after their recognition of antigens in the context of major histocompatibility complex molecules on other cells, is also being clinically tested in prostate cancer patients. Antibodies blocking checkpoint molecules CTLA-4 and PD-1 or PD-1 ligand molecule PD-L1 have recently obtained FDA approval for the treatment of melanoma, non-small cell lung cancer, renal cell cancer, urothelial cancer, head and neck cancer and Merkel-cell carcinoma. However, the results to date reveal that, when used as monotherapy, the CTLA-4 or PD-1 blockade alone plays a minor role in the treatment of patients with prostate cancer (10-15).

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