The Up to Date Progress of Prostate Cancer Vaccines

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Abstract. The prostate cancer vaccine has significant influences on males, and the cancer among American men has second highest prevalence among all cancers. Both the prevalence and mortality rates of prostate cancer in America are increasing each year. Researchers have been working to improve and innovate the way prostate cancer is diagnosed and treated. One promising direction is immunotherapy. Scientists have been working on a vaccine for prostate cancer for decades, and FDA only passes Sipuleucel-T as prostate cancer vaccine, but many other prostate cancer vaccines have been developed. Therefore, after synthesizing many papers, this paper explains the principles, latest progress, the advantages and disadvantages of all the vaccines developed so far, and proposes that future researchers should improve the prostate cancer vaccine in the direction of combination therapy, and conduct in-depth research to explore the prostate cancer vaccines that are currently showing an excellent trend, and to optimize the Sipuleucel-T.

Keywords: Immunotherapies, prostate cancer vaccine, combination therapy.

1. Introduction

The population in America suffering with prostate cancer is incessantly increasing , resulting in it being the second most common cancer. An estimated tens of thousands of people die from prostate cancer each year. Even though there are significant advances in diagnostic methods (e.g., MRI, PSA, etc.), prostate cancer mortality remains high. China had a mortality rate of 4.19 per 100,000, a winning rate of 1.58 per 100,000, and a world rate of 2.58 per 100,000[1]. To date, prostate cancer has been treated with a variety of therapies, such as surgery, radiotherapy, chemotherapy, ACT, and immunotherapy. However, immunotherapy, as a hot topic, holds great promise in prostate cancer treatment. Researchers have been working on prostate cancer vaccines for decades now. FDA only passes the cancer Sipuleucel-T about prostate cancer until now, but the vaccines that have been developed to treat prostate cancer besides Sipuleucel-T are GVAX-PCa, DCAVAC/PCa, PSA, PSA-TRICOM (PROSVAC), GX301, Individualised peptide vaccines, DNA/mRNA vaccine and AE37 vaccine. This article explains the rationale of the listed vaccines, the latest progress, the advantages and disadvantages, and the future research trend of combination therapy. GVAX-PCa was shown to be effective in two of the phaseIII trials, but two trials were halted due to GVAX-PCa's failure to improve survival and mortality dysregulation in prostate cancer patients. The DCAVAC/PCa trials were less and less therapeutically effective. Three stages of trials were conducted on PSA, but there are few phaseIII trials now. PhaseIII trials resulted in the discontinuation of pROSVAC due to unsatisfactory results. PPV was also tested in three phase trials. GX301 is now tested in first two phase trials. Anti-prostate cancer mRNA vaccines are still under further investigation. Although there have been fewer trials, the Interferon- -modified exosomal vaccine and the AE37 vaccine have consistently shown favorable trial results.These cancer vaccines have acommon advantage: they have a certain safety profile.

2. Discussion

2.1. Monocyte-based vaccines: Sipuleucel-T

Sipuleucel-T, is therapeutic vaccine to treat with prostate cancer. FDA only passes Sipuleucel-T until now. It is a new type of autoimmune cell therapy, which allows men to live longer. The objective is to focus on the men with metastatic drug-fast prostate cancer, which is either asymptomatic or

minimally symptomatic. Immune system was activate in patient to fight tumors. The main active components are antigen-presenting cells that are activated by prostatic acid Phosphatase Recombinant Protein and Granulocyte-macrophage Colony-stimulating Factor Recombinant Protein. PAP can be divided into two forms. One is the cellular form, which is expressed in the cells of prostate, the other one is the secreted form being exclusive to the prostate[2]. It passes through the prostate duct into the seminal vesicle and is discharged from the urethra. It can serve as a kind of index to prostate cancer because the PAP produced by cancer cells in the prostate may be absorbed into the blood cycle and then cause an increase of serum prostatic acid phosphatase when people suffer from prostate cancer. GM-CSF is an immune system that is activated by cytokines, The polymerization of these fusion proteins leads to the training and activation of APCs collected by them. When a patient's APCs are processed with PAP-GM-CSF in vitro, GM-CSF presents antigenic fragments on its surface. After the patient completes the provenge injection, the provenge activates T-cells in the patient and rapidly multiplies them. A specific and lasting immune response is caused by activated targeted T-cells and attacked prostate cancer cells that express PAP antigen from the immune system. This mechanism is followed by two additional cycles of autologous therapy in the patient's body over a month, as this allows the patient to fight off advanced prostate cancer. In clinical trials, most patients present with adverse symptoms such as fatigue, fever, arthralgia, back pain, chills, nausea, and headache. APC activation and immune enhancement are two of Sipuleucel-T's specific mechanisms. Improvements in OS are statistically significantly associated with an increase in cumulative APC activation[3]. Among different species, the prostates are totally different, which increases the difficulties for scientists to directly exert the result of animal trials on humans. Researchers discovered that the immunized rats with antigens from rat prostate tissue caused destructive prostatitis before launching Sipuleucel-T's clinical trials, using a rat APC preparation that existed PAP and GM-CSF caused prostatitis in rats. Despite this, there was no indications of toxicity to normal non-prostatic tissue[4]. In both studies, it has been suggested that it could defeat common immune tolerance and cause autoimmunity in the tissue of prostate. The foundation for a clinical trial of a vaccine similar to this one for prostate cancer is laid in this animal study. In phaseI trial, sipuleucel-T increased its doses to the patients. The leukapheresis product which prepared as patients accepted sipuleucel-T in phaseII protocol with a full dose[4]. In patients, fever and tumor response were the most common adverse reaction, and only 20% of patients decreased prostate-specific antigen levels from baseline[4]. Additionally, fusion protein has a linker area fragment which isn't showed by normal PAP, it can not be showed by GM-CSF too. Thus, the patient's immune system can identify it as foreign. A marker of immunocompetence is expected to be triggered by exogenous linker area fragment's immune response, but it is likely not related to treatment outcome. The detection of PAP immunity is the potential marker which is more significant of immune response with the attribute--therapeutic. The results of another efficacy trial were comparable for a vaccine that contained autologous CD54-positive PA2024 APC. CD54 is responsible for the activation of APC and other leukocytes[4]. Before third phase IMPACT experiment, the D9901 and D9902A phaseIII trials against asymptomatic the trials in asymptomatic mCRPC patients are also of particular importance. The survival rate that is average for sipuleucel-T in the first PhaseIII trial was 112 weeks compared to 93 weeks for controls. Overall survival increased by 4.5 months as a result of sipuleucel-T[2]. D9902A, on the other hand, improved the results of the first trial and other related trials. In sipuleucel-T group, the average survival was extended again compared to the control group, and the survival rate for the 3-year period increased by 50%[2]. The sipuleucel-T and placebo trial groups were randomly assigned to about 500 patients in this trial. The result was that the sipuleucel-T group experienced a 22% increase the possibility of death than the placebo group[3]. Another research examined the influences of sipuleucel-T, and predictor to detect function was baseline PSA[5]. The effectiveness of Sipuleucel-T was greatest for patients with a lower predicted risk of progression. The better the treatment result, the earlier Sipuleucel-T was administered[3]. However, sipuleucel-T has not been used in wide rage in real life, both because sipuleucel-T has a low clinical success rate and because it is expensive, making it unacceptable to many patients. The vaccine has stopped producing in Europe because it's

too complicated to manage and has low survival benefit and high price[6]. Despite its survival benefit, it can be only found the weakest anti-tumor responses after patients receive the vaccine[7]. However, recently, a study showed that IL-15 treatment enhances sipuleucel-T's efficacy and anti-tumour immunity through regulating CD8+T cells and CD56+NKT subpopulations which provides another direction for researchers to invest[8].

2.2. Cancer cell vaccine: GVAX-PCa

GVAX is a cellular vaccine based on a prostate cancer cell line that uses genetic technology to cause tumour cells to express the protein factor GM-CSF, which stimulates the action of immune cells against cancer cells. 55 patients without receiving chemotherapy were vaccinated with GVAX-PCa in phase I/II trials, and autoimmune toxicity was not detected[9]. In phase I/II, the vaccine demonstrated well toleration in the dose-escalation study among 80 patients with metastatic prostate cancer, the most common side reaction was erythema being [10]. Phase I showed that GVAX-PCa is very safe and can increase the survival length of patient if boosted at high doses[9]. GVAX-PCa and ipilimumab's combination has stated the investment in phase I clinical trial. The two phaseIII trials have illustrated that ipilimumab alone can enhances patients' OS with metastatic melanoma[9]. However, both VITAL-1 and VITAL-2 trials were forced to stop because they failed to improve survival and mortality dysregulation in prostate cancer patients, respectively. In summary, GVAX-PCa has demonstrated its strengths in both early trials by having a high safety rate and also demonstrating anti-tumor activity. Unfortunately, GVAX-PCa has hardly progressed since the latter two trials did not show the expected results.

2.3. Dendritic cell vaccine: DCAVAC/PCa

DCAVAC/PCa is a kind of autologous vaccine, it composed of one specific dendritic cells which can be provoked though inactive Psa-positive LNCaP cells[10]. 25 mCRPC patients were vaccinated with DCAVAC/PCa in first two phase trials, which concluded that DCAVAC/PCa has a safety profile. The third research trial (VIABLE) was a phase III study hypothesized to be a combination of doxorubicin and DCVAC/PCa.DCAVAC/PCa has the advantage of being able to tailor the treatment to the patient's specific situation, but there are fewer trials of DCAVAC/PCa, and there are no more significant therapeutic results.

2.4. Viral vaccines

2.4.1 Adenovirus /PSA

Adenovirus /PSA belongs to one of the most valid ways for the delivery in vivo gene[11]. In clinical studies, Ad5-PSA and the collagen matrix Gelfoam®'s combination kept viral vectors away from anti-adenoviral antibodies' high titers, it led to a stronger immune response than Ad5-PSA alone[12]. During PhaseI trial, the chosen patients were administered Ad5-PSA and met the primary endpoint of establishing safety. The adverse events were slight, also, many of them were transient[9]. In the Phase II study, the investigators improved by administering the vaccine three times, one month apart, with no final results to date. There are few relevant phase III trials.

2.4.2 PSA-TRICOM (PROSVAC)

PROSTVAC is an off-the-shelf vaccine with PSA as the target antigen. The immune response was triggered by combining recombinant cowpox strain with a foxtrot vector enhancer, a co-stimulatory molecule and a transgene[13]. Above 300 prostate cancer patients were treated in PROSTVAC's Phase 1 and Phase 2 trials successfully The result showed it is well tolerated. Compared to the trial of Sipuleucel-T, PROSTVAC could extend 4.1 months about the prostate cancer patients' median survival[14]. Originally, the results in first two phase I trials were exciting and even drew keen attention from the cancer vaccine community. However, the phase III trial stopped because the results weren't good[15]. The advantages were shown to be the absence of toxicity, but the benefits in terms of increased survival time were minimal.

2.5. Peptide vaccine

2.5.1 GX301

GX301 is composed of telomerase peptides and immune adjuvants[3]. PhaseI and II trials showed its safety and immunological efficacy. To patients with mCRP, GX301 vaccine has little negative effects. Future studies can benefit from the fact that the immune response rate is linked to immunizations' population [3].

2.5.2 Individualized peptide vaccines(PPV)

PPV is the vaccine based on immunity before vaccination to select and use HLA-matched peptides [16]. Major histocompatibility complex received specific tumor antigenic peptides on the surface of APCs through PPV's mechanism, where T cells recognize the peptide-MHC-TCR complex formed by degradation to short peptides in APCs[3]. One PPV phaseII trial with CRPC patients showed that combined PPV with low-dose estramustine phosphate (EMP), patients had longer freedom from progression[16]. In PhaseIII trial, RESEARCHERS injected a number of prostate cancer patients who had been cured with docetaxel chemotherapy with PPV, and their results showed OS in patients in the PPV trial.

2.6. DNA/mRNA vaccine

DNA vaccines follow the principle that a recombinant eukaryotic expression vector encoding a protein antigen is injected directly into an animal so that the exogenous gene is expressed in vivo and the resulting antigen activates the immune system, thus inducing specific humoral and cellular immune responses. No adverse effects were detected in the vaccinated patients, and 41% (9/22) of patients had a proliferation of PAP-specific (CD4+ or CD8+) T lymphocytes during phase I/II clinical study. Likewise, phaseI trial encoding DNA-PSA, pVAX/PSA could induce PSA-specific humoral and cellular immune responses [9]. Most of patients showed elevated PSADT, also, their cancer status were not erratic[9]. DNA vaccines have the advantages of being easy to use, safe, easy to manufacture, and non-infectious, but the use of naked DNA-based vaccines may be limited by low transfection efficiency.

The mRNA vaccine introduces mRNA encoding antigenic proteins into human body, and then form the corresponding antigenic proteins by translating it directly, so as to induce the body to produce a specific immune response and achieve the effect of preventive immunity. The mRNA vaccines against prostate cancer are still under further research.

2.7. AE37 vaccine

The adjuvant in phaseI trial combines AE37 and granulocyte/macrophage colony-stimulating factor, researchers successfully immused prostate cancer patients[17].The trial showed that the low toxicity and high toleration of AE37 vaccine. The immune response of vitro against AE37 vaccine cis related to the improvement of OS[17].

2.8. New trends

All prostate cancer vaccines have the common advantage of being safe, but they do not show any major advantage over other prostate cancer treatments. Vaccines to treat prostate cancer can adopt combination therapy some time, i.e., combining other prostate cancer treatment modalities such as medication, chemotherapy, etc. with cancer vaccines. For example, research has proved that the combination of vaccine in plasmid DNA vaccine and PD1 blockade can produce a better anti-cancer effect. Furthermore, pVAX/PSA was found to induce PSA-specific humoral and immune responses in cells in a DNA-PSA phaseI trial[8]. Of course, researchers should not only continue to optimize Sipuleucel-T, which has a great contribution to prostate cancer immunotherapy but also further explore other prostate cancer vaccines that are currently showing good trends in trials. For example, mRNA/DNA vaccines have shown good results in trials, and such vaccines are also of great use in other diseases.

3. Conclusion

The Prostate cancer vaccines mentioned in this paper have been shown the secure to prostate cancer patients. Rather than other treatments for prostate cancer, prostate cancer vaccines have not shown a significant advantage so far. Some trials have shown promising results when prostate cancer vaccines are combined with other treatment modalities like drugs and chemotherapy. Therefore, researchers can focus the main future trend of prostate cancer vaccines on combination therapy to maximize the anti-cancer cell effect of prostate cancer vaccines. Of course, researchers should not only continue to optimize Sipuleucel-T, which has made a great contribution to prostate cancer immunotherapy but also further explore other prostate cancer vaccines that are currently showing good trends in trials. For example, mRNA/DNA vaccines have shown promising results in trials, and these types of vaccines have great uses in other diseases, so mRNA/DNA vaccines deserve to be explored in depth by researchers. It is hoped that with researchers investing in the exploration of prostate cancer vaccines, vaccines that can allow prostate cancer patients to survive longer, minimise the impact of daily life or even completely cure prostate cancer, and reduce the prostate cancer mortality rate, can be created shortly.

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