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Cancer Vaccine in Solid Tumors: Where We Stand

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Abstract

Cancer immunotherapy has achieved landmark progress in the field of medical oncology in the era of personalized medicine. In the recent past, our knowledge has expanded regarding how tumor cells escape from the immune system, introducing immunosuppressive microenvironments, and developing tolerance. Therapeutic cancer vaccine leads to activation of immune memory that is long-lasting, safe, and effective; hence, it is becoming an attractive method of immunotherapy. Various cancer vaccine trials in the past have taught us the types of target selection, magnitude of immune response, and implementation of appropriate technologies for the development of new successful cancer vaccines. Tumor-associated antigens, cancer germline antigens, oncogenic viral antigens, and tumor-specific antigens, also known as neoantigens, are potential targets for designing therapeutic cancer vaccines. Cancer vaccine could be cell based, viral vector based, peptide based, and nucleic acid based (DNA/RNA). Several preclinical and clinical studies have demonstrated the mechanism of action, safety, efficacy, and toxicities of various types of cancer vaccines. In this article, we review the types of various tumor antigens and types of cancer vaccines tested in clinical trials and discuss the application and importance of this approach toward precision medicine in the field of immuno-oncology.

Keywords
- immunotherapy
- solid tumors
- therapeutic cancer vaccine
- tumor antigen

Introduction

Cancer immunotherapy and its application in solid tumors have revolutionized the field of immuno-oncology in the recent past. Several immune checkpoint inhibitors (ICIs) that modulate the function of PD-1, PD-L1, and CTLA-4 have demonstrated a significant clinical benefit in several tumors, particularly in nonsmall cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), bladder tumor, breast cancer, etc. Various adoptive cellular therapies, particularly chimeric antigen receptor T (CAR-T) cell therapy in acute lymphocytic leukemia (ALL) and tumor-infiltrating T-lymphocyte therapy in melanoma, have also produced remarkable responses. These breakthroughs have proven the feasibility and efficacy of cancer immunotherapy and opened new ideas to develop other therapies. Development of therapeutic cancer vaccines is another remarkable milestone achieved in this field. Several clinical trials yielded a disappointing result regarding the application of therapeutic vaccines when tested in different types of cancers. Low immunogenicity and the immunosuppressive effect of tumor microenvironment are the major challenges against the successful development of therapeutic cancer vaccines. On the contrary, prophylactic cancer vaccines such as human papillomavirus (HPV) vaccine in cervical

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cancer and hepatitis B virus (HBV) vaccine in hepatocellular carcinoma (HCC) are successful achievements.[1]

Here, we summarize the different types of tumor antigen targets for the development of cancer vaccines and various types of vaccines tested in clinical trials along with future strategies in this field.

Tumor Antigens for Cancer Vaccine

There are mainly four categories of tumor antigen targets for the development of cancer vaccine. Out of them, neoantigens are the most potential targets for therapeutic cancer vaccines. Here, we describe each entity briefly.

Tumor-Associated Antigens

Tumor-associated antigens (TAAs) are self-antigens that are abnormally expressed in tumor cells and to some extent expressed in normal cells too. T-cells recognize these TAAs as self-antigens and by the activation of central and peripheral immune tolerance mechanisms, these are deleted from the immune system. For this reason, cancer vaccines using these antigens must be potent enough to break immune tolerance. Targeting TAAs in the development of vaccine met with limited success as these are normal host proteins and destroyed by central and peripheral tolerance.[2] Various autoimmune toxicities such as hepatitis, renal impairment, colitis, and respiratory failure also occurred due to targeting these TAAs.[3] Several TAAs like; CD-19 expressed on B cell malignancies and ERBB-2 on breast cancer cell are potential targets of CAR-T cell therapy leads to on target but off tumor side effects because these TAAs are also expressed on normal cells.[4-6] It has shown a significant response in some ALL, but there had been huge challenges to treat solid tumors due to lack of suitable TAAs.[4,5] The reported overall objective response rates of CAR-T cell therapy for solid tumors are still low.[7,8]

Cancer Germline Antigens

Cancer germline antigens, also called cancer/testis antigens (CTAs), are immunogenic proteins encoded by genes that are normally expressed in gametes and trophoblast and also expressed in various cancer cell lines such as melanoma and carcinomas of the bladder, lung, and liver.[9,10] They are being evaluated as targets for therapeutic cancer vaccines. Melanoma-associated antigen 3 (MAGE-A3) is a type of CTA encoded by the MAGE-A gene family expressed in common epithelial malignancies including esophageal cancer and melanoma. Morgan et al treated nine patients with adoptive cell therapy using autologous anti-MAGE-A3 T cell receptor-engineered T-cells, but severe neurological toxicity and death led to failure of this approach.[11]

Oncogenic Viral Antigen

Viruses most commonly associated with human malignancies are Epstein–Barr virus, HBV, HCV, HPV, Kaposi's sarcoma herpesvirus, and human T cell lymphotropic virus-1. The development of prophylactic vaccines against these viral-encoded antigens effectively reduces the risk of virus-associated cancer.

HCC due to chronic HBV infection has been effectively prevented by HBV vaccination. Taiwan is a hyperendemic area for HBV infection, where the majority of adult HCC cases are due to HBV infection. HCV infection also plays an important role in the prevalence of HCC in different geographic areas of Taiwan.[12] There was a significant reduction in HCC by implementation of a nationwide HBV immunization program among Taiwanese population.[13]

Several HPV subtypes such as HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are the major causes of carcinomas of the cervix, oropharynx, and anogenital regions. Viral E6 and E7 oncoproteins expressed within the infected cell are subsequently processed and presented to stimulate cytotoxic T-cells and augment immune response. Apart from bivalent (Cervarix) and quadrivalent (Gardasil) HPV vaccine, recently, a nonavalent vaccine (Gardasil-9) that covers five additional HPV genotypes (31, 33, 45, 52, and 58) has been approved by the U.S. Food and Drug Administration (FDA) for the prevention of both cervical cancer and genital warts.[14]

Tumor-Specific Antigens

Tumor-specific antigens, also called neoantigens that arise from cancer-specific several genomic mutations, represent another class of attractive antigens for therapeutic vaccine. These neoantigens are mutated peptides that have been presented by antigen presenting cells (APCs) and our immune system recognize these neoantigens as foreign; leads to activation of Tcells. Activated T-cells undergone proliferation and infiltrate to the tumour microenvironment. As normal cells do not express these Tumor- Specific Antigens (TSAs), they are being escaped from central and peripheral tolerance and less likely to induce autoimmunity. These are the distinct advantages of neoantigens renders potential targets for adoptive cell therapy and therapeutic vaccine.[1,15,16]

Categories of Cancer Vaccines

For cancer immunotherapy, mainly three different target methods are used for vaccine development: cellular vaccines, viral vector vaccines, and molecular vaccines composed of peptides, DNA, and RNA.

Cellular Vaccines

Cellular vaccines are developed from either killed cancer cells or autologous antigen-presenting cells (APCs) loaded with cancer antigen. Dendritic cells (DCs), most potent professional APCs, collect antigens from various tissues and transport them to secondary lymphoid organs, which in turn activate antigen-specific T-cells.[17] DCs also uptake, process, and present tumor antigen to naïve T-cells in lymphoid organs, required for the induction of immunological tolerance and regulation of T cell-mediated immune response.[18] Sipuleucel-T is the prototype of DC-based vaccine (targeting ex vivo antigen delivery to DCs), whereas GVAX and Canvaxin are whole-cell vaccination approaches tested in clinical trials.[17]

Sipuleucel-T (Provenge, Dendreon)

Sipuleucel-T (Provenge) targets prostatic acid phosphatase (PAP) that is highly expressed in prostate cancer cells. The exact mechanism of action of this vaccine is unknown. It develops using APCs incubated with recombinant fusion protein antigen containing PAP and granulocytic macrophage colony-stimulating factor (GM-CSF). These antigen-loaded activated APCs stimulate T cell-mediated immune response against prostatic cancer cells. Sipuleucel-T is the first FDA-approved therapeutic cancer vaccine used in metastatic castrate-resistant prostate cancer (mCRPC).

IMmunotherapy for Prostate AdenoCarcinoma Treatment, a Phase III trial, which randomized 512 mCRPC patients at 2:1 to receive sipuleucel-T or placebo, administered intravenously every 2 weeks, for a total of three infusions, demonstrated a median overall survival (OS) benefit of 4.1 months (25.8 vs. 21.7 months) (hazard ratio [HR]: 0.751; 95% confidence interval [CI]: 0.606–0.951; $p = 0.017$).[19] The most common adverse events associated with the sipuleucel-T group were infusional reactions such as chills, fever, and headache due to release of cytokines.[19] Lack of availability, high cost, and complexity of producing sipuleucel-T create an obstacle to its routine use.

DCVax (Northwest Biotherapeutics)

DCVax is a family of DC-based vaccine consisting of autologous DCs recombinant with various TAAs. There are three separate DCVax platforms: (a) DCVax-Prostate, (b) DCVax-L, and (c) DCVax-Direct. DCVax-prostate uses DCs fused with recombinant prostate-specific membrane antigen whole protein, whereas DCVax-L was developed from differentiated DCs pulsed with autologous whole tumor lysate.[20]

Previously reported Phase I/II trials on DCVax-L showed a survival benefit in newly diagnosed or recurrent glioblastoma multiforme (GBM).[21] Subsequently, a Phase III trial was initiated to evaluate the addition of DCVax-L to standard of care for newly diagnosed GBM. After surgery and chemoradiotherapy, patients were randomized at 2:1 to receive temozolomide plus DCVax-L or temozolomide with placebo, demonstrating modest survival benefit with feasibility and safety of this approach.[22]

GVAX

GVAX vaccine is the genetic modification of whole tumor cells to secrete immune-stimulatory cytokines and GM-CSF that leads to recruitment, differentiation, and activation of DCs at injection sites. These activated DCs subsequently process the tumor antigens and present these antigens to T-cells with trafficking of T-cells into draining lymph nodes to elicit antitumor immune response.[23]

When GVAX has been tested in hormone refractory prostate cancer, high-risk surgically resected melanoma in adjuvant settings, advanced pancreatic cancer and metastatic NSCLC, it showed limited efficacy despite stimulating immune response.[24,25,26,27] Two Phase III studies, the VITAL-1 and VITAL-2 in metastatic prostate cancer, were terminated early due to lack of therapeutic effect.[28] Despite disappointing results in prostate cancer, one randomized Phase II trial in metastatic pancreatic cancer; GVAX improves survival with acceptable side effects.[29]

Rocapuldencel-T (ASG-003)

Rocapuldencel-T is a DC-based co-electroporated vaccine developed ex vivo from two types of RNA, the patient's amplified tumor RNA and synthetic CD40 L RNA, and it is tested in RCC. In a Phase II trial, 25 patients with metastatic RCC (mRCC) were given rocapuldencel-T in addition to planned sunitinib therapy. The trial demonstrated roughly doubling of the expected survival where 24% of patients survive more than 5 years with nominal toxicities.[30] The promising result of this Phase II trial initiated a Phase III trial (ADAPT) that randomized patients with advanced or mRCC (clear cell type) to sunitinib with or without rocapuldencel-T in a 2:1 fashion. It failed to show a significant OS difference between groups (HR: 1.10, 95% CI: 0.83–1.40) but helped to identify two potential biomarkers for future DC-based immunotherapeutic intervention and prolongation of survival.[31] Validating the effectiveness of the combination of rocapuldencel-T with standard therapy needs more mature data and long-term follow-up.

Viral Vector Vaccines

Viral vector vaccines are naturally immunogenic. They are developed by inserting recombinant plasmid codes for TAAs into the viral genome, sometimes along with a plasmid coding for an immunoadjuvant or cytokines. The viral proteins injected into the human body induce a strong immune response by recruitment of APCs.

ProstVac-VF (Bavarian Nordic)

ProstVac-VF is a good example of a genetically engineered recombinant viral vaccine. It is composed of two forms, ProstVac-V (vaccinia virus-PSA) and ProstVac-F (fowlpox virus-prostate-specific antigen [PSA]), administered in a sequential regimen to treat prostate cancer. A triad of costimulatory molecules (referred to as *TRICOM*) was added to the vaccine along with B7–1 and ICAM-1.[32] A Phase I trial vaccination with ProstVac-V followed by ProstVac-F combined with *TRICOM* was tested in prostate cancer.[32]

In a phase II randomized trial, 125 men with mCRPC; ProstVac-VF yielded a significant median OS benefit for intention to treat population compared with control group (26.2 Vs 16.3 months).[33] However, subsequently, in a Phase III trial, these combinations failed to show OS benefit, leading to interim stoppage of the trial.[34] ProstVac-VF is now being tested in combination with several ICIs.

TroVax (Modified Vaccinia Strain Ankara-5T4)

TroVax is a modified vaccinia strain Ankara-based vaccine, to express onco-fetal antigen 5T4, present mainly in RCC, rectum, ovary, prostate, breast, and colon.[35] A Phase III study of 732 patients of mRCC prior nephrectomy was randomized in a 1:1 fashion to receive vaccine or placebo in combination with standard of care. Although this combination was well tolerated, no difference in OS was observed in the entire cohort. A subgroup analysis revealed that patients with high

5T4-specific antibodies had favorable outcomes (HR: 0.55, 95% CI: 0.39–0.97).[36]

Peptide Vaccines

Protein-based peptide vaccines act via the normal pathway of antigen uptake, processing, and presentation by APCs to elicit immune response against various TAAs. They are of three types: single peptide, multiple peptide, and full protein vaccine.

Nelipepimut-S (Galena Biopharma)

Nelipepimut-S (E75) is a peptide vaccine derived from HER2 protein present in breast cancer cells to produce specific immune responses. Based on a Phase I/II trial where patients with high-risk breast cancer receiving the vaccine had improved disease-free survival, a Phase III (PRESENT) study started in 2014 compared nelipepimut-S versus GM-CSF in patients with node-positive HER2 low-expressing breast cancer. This trial was stopped due to futility in June 2016 after an interim review.[37,38]

Glycoprotein 100

This vaccine was developed using melanoma-specific immunogenic peptide of glycoprotein 100 (Gp100) (amino acids 209–217) in combination with an immune-adjuvant Montanide ISA-51. A Phase II trial was conducted using Gp100 with interleukin (IL)-2 combination, which showed an improved objective response rate compared with that of the previous result of IL-2 alone.[39] A Phase III trial was organized that randomized 177 patients of Stage III/IV melanoma to IL-2 alone or combination regimen. Addition of vaccine showed a higher clinical response rate (16 vs. 6%; p = 0.03) and prolonged progression-free survival (PFS) (2.2 vs. 1.6 months; p = 0.008).[40]

Tecemotide (Cascadian Therapeutics)

Tecemotide (L-BLP25) is a mucin 1 (MUC1 glycoprotein expressed in NSCLC) antigen-specific peptide vaccine, capable of inducing cell-mediated immune response against MUC1 protein that was tested in preclinical studies. After promising results in a Phase II trial, a randomized Phase III trial (START) was initiated among patients with unresectable Stage III NSCLC, after chemoradiation as a maintenance therapy with this vaccine.[41] The median OS was similar between both groups (25.6 vs. 22.3 months, HR: 0.88; p = 0.123), but vaccinated patients showed an improved secondary end point of time-to-symptom progression (HR: 0.85; p = 0.023). A subgroup analysis revealed a significant improvement of median OS of those who received previous concurrent chemoradiation (30.8 vs. 20.6 months, p = 0.016).[41]

Rindopepimut (Rintega)

Epidermal growth factor receptor variant III (EGFRvIII) is a type of deletion mutation of EGFR often overexpressed in primary GBM patients. Rindopepimut (CDX-110) is a peptide vaccine that spans the length of EGFRvIII, conjugated with carrier protein keyhole limpet hemocyanin. A Phase II trial (ACT III) with newly diagnosed GBM showed an increase in PFS and OS among vaccinated patients over historical control, but a subsequent Phase III trial found discouraging result.[42,43]

Belagenpumatucel-L (Lucanix)

Belagenpumatucel-L is a vaccine produced from irradiated allogeneic NSCLC cells transfected with transforming growth factor β-2 antisense gene plasmid. In a dose variable, randomized Phase II trial, 75 patients with Stage II, IIIA, IIIB, and IV (AJCC 6th edition) NSCLC received one of the three doses of vaccine (1.25, 2.5, or 5 × 10^7 cells/injection). A dose-related significant survival difference was seen among patients who received 2.5 or 5 × 10^7 cells per injection (p = 0.0069).[44] Later on, a phase III randomized trial was conducted with stage III-IV NSCLC patients who did not progress after platinum based chemotherapy, to receive maintenance Belagenpumatucel-L or placebo. The median survival was similar among the overall cohort (20.3 months for vaccine group vs. 17.8 months for placebo, p = 0.594), but subgroup analysis revealed that patients receiving vaccine within 12 weeks of completion of chemotherapy had a longer median survival (20.7 vs. 13.3 months, p = 0.092).[45,46]

DNA and RNA Vaccines

Genetic vaccine has become the fastest-growing field in vaccine technology using DNA (as a plasmid) or RNA (as mRNA) that is taken up by APCs and translated into protein as cancer-specific antigens to induce antitumor immunity. Transfected cells express the antigen encoded on plasmid DNA to APCs, effectively engaging both major histocompatibility complex (MHC-I) and MHC-II pathways with recruitment of $CD8^+$ and $CD4^+$ T-cells, resulting in an immune response.[47]

There are different kinds of genetic vaccines tested in several clinical trials such as PAP for prostate cancer, mammaglobin-A DNA vaccine for breast cancer, human tyrosinase-related protein 1 also called gp75 glycoprotein (Tyrp1/gp75) for melanoma, and VXM01, an oral T cell vaccine against vascular endothelial growth factor receptor 2 for advanced pancreatic cancer.[48-51] The most dramatic approach to improve the immunogenicity of genetic vaccine is by introducing the property of "self-replication." It is accomplished by using gene-encoded alphavirus RNA replicase, an autoproteolytic polyprotein, which promotes enormous RNA replication in the cytoplasm of infected cells, particularly positive-strand "subgenomic" mRNA for the encoded antigen. Antigens released from the transfected cells are presented to APCs to enhance immune response via MHC-I complex, interferon release, and proinflammatory dsRNA.[47] The nanoparticulate RNA immunotherapy approach introduced RNA-lipoplex (RNA-LPX) vaccine, encoding viral or mutant neoantigens or endogenous self-antigens, to induce strong antitumor immune response tested in a Phase I trial in advanced melanoma.[52]

Conclusion

Therapeutic cancer vaccines lead to activation of immune memory that is long lasting, safe, and effective and hence has become an attractive method of immunotherapy. Tumor-specific neoantigens that have the lowest risks of autoimmunity are preferred therapeutic targets for the development of cancer vaccine. Although many previous trials of therapeutic cancer vaccines failed to show promising results, currently several ongoing studies have been showing attractive clinical outcomes.

In addition, a combination of ICIs, chemotherapy, or radiotherapy with cancer vaccines that reverse immunosuppression and augment antitumor immunity has demonstrated promising results in several ongoing trials. However, further research is needed to determine which combinations have the best efficacy and safety. Hopefully, continuous research works and expansion of our knowledge in the field of immuno-oncology will help most of the cancer patients in the near future to be treated with effective and affordable personalized therapeutic cancer vaccine.

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Conflicts of Interest
There are no conflicts of interest.

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