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CANCER IMMUNIZATION WILL THIS TURN OUT TO BE A PLUS? IMMEDIATELY GRASPABLE

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Abstract
The first cancer vaccine using tumor cells and lysates was created in 1980. The COVID-19 pandemic has revitalized interest in cancer vaccines and accelerated their development. Finally, mRNA vaccines can be made rapidly and affordably. RNA-stimulated dendritic cells were the focus of the first mRNA-based cancer vaccine study, which was conducted in 1996. Clinical trials of several cancer immunotherapy vaccines have shown encouraging results. Therapeutic cancer vaccine efficacy is affected by several factors, such as the selected target antigen(s), the presence of adjuvants, and the vaccine's capacity to elicit antitumor T cell responses in a highly immunosuppressive tumor microenvironment.

Keywords:- Lung cancer vaccine, Oral cancer vaccine, Human papillomavirus (HPV) vaccine, and other cancer vaccines

Introduction

The development of vaccines has opened up promising new avenues for the prevention and treatment of infectious diseases. Edward Jenner's discovery that a cowpox vaccine could prevent smallpox was the first vaccine ever developed, in 1796. As the vaccine progressed, it was used to combat an expanding array of illnesses, cancer included. A vaccine against cancer using tumor cells and tumor lysates was developed for the first time in 1980. The use of autologous tumor cells in the treatment of colorectal cancer was recently discovered. It wasn't until the discovery of melanoma-

associated antigen in the early 1990s that the use of tumor antigens in cancer vaccines became a realistic possibility. Successful treatment of prostate cancer with a dendritic cell-based vaccine (Sipuleucel-T) in 2010 proved the efficacy of cancer vaccines and sparked significant interest in this promising field. The COVID-19 pandemic has revitalized interest in cancer vaccines and accelerated their development.[1] Cancer vaccines rely heavily on tumor-associated antigens (TAAs) and tumor-specific antigens to elicit an immune response from the patient (TSAs). The vaccine has the potential to prevent tumor growth and wipe out cancer cells by stimulating both cellular and humoral immune responses. Most cancer vaccines have not even reached the clinical testing phase yet. Antigens and vaccine development platforms need to be refined to be more targeted. As a result of the COVID-19 epidemic, researchers around the world are looking more closely at mRNA-based vaccines. Indeed, years of study exploring mRNA vaccines as a treatment strategy for cancer laid the groundwork for the swift development and production of the COVID-19 vaccine in both preclinical and clinical trials. Using just one mRNA in a vaccination context has many benefits . A primary advantage of mRNA-based vaccines is that they do not integrate into the host genome, are rapidly degraded, and are well tolerated , mRNA molecules don't spread disease, and vaccines based on them can generate protective immune responses in both the immune system's humoral and cellular arms. Finally, mRNA vaccines can be made rapidly and affordably. RNA-stimulated dendritic cells were the focus of the first mRNA-based cancer vaccine study, which was conducted in 1996. Intra dermal, Subcutaneous, Intranasal, Intra nodal, Intramuscular, Intra tumoural and intravenous administration are all viable options for mRNA vaccines, and multiple clinical trials are currently enrolling cancer patients for mRNA-based vaccine therapies. However, most mRNA vaccine strategies focus on direct mRNA administration via lipid nanoparticle formulation carriers, despite the fact that ex-vivo engineering of autologous dendritic cells with mRNA has been the preferred method for tumor antigen delivery.[2]

Cancer immunotherapy falls into two main categories, passive and active, depending on their mechanism of action. Passive immunotherapy aims to boost already present antitumor responses by using therapeutic agents like targeted antibodies, lymphocytes (e.g. adoptive cell transfer [ACT] of ex vivo propagated tumour-infiltrating lymphocytes or engineered chimeric antigen receptor [CAR] T cells), cytokines, adjuvants, and immune checkpoint inhibitors. Patients with advanced cancer who experienced durable tumor regression after ACT provide clinical evidence for the efficacy of such therapies. T-lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1) and their ligands (B7 and PDL-1/2) on antigen-presenting cells (APCs), stromal cells, and tumor cells have been shown to be particularly effective immune checkpoint inhibitors in melanoma and lung cancers, among others. In contrast, the goal of active immunotherapy with cancer vaccines is to train the immune system to recognize and kill cancer cells and to create an immunological memory that will allow for the long-term suppression of tumor growth. Clinical trials of several therapeutic cancer vaccines have shown encouraging results. Therapeutic cancer vaccine efficacy is affected by several factors, such as the selected target antigen(s), the presence of adjuvants, and the vaccine's capacity to elicit antitumor T cell responses in a highly immunosuppressive tumor microenvironment. A beneficial and relevant antitumor T cell repertoire can be induced in individual cancer patients through the use of personalized cancer vaccination. Due to their extensive genetic instability, tumor cells can express a wide variety of abnormal proteins with either restricted (such as TAAs) or no expression (such as de novo mutated tumor neoantigens) on normal cells. Cancer vaccines may one day aim for these tumor-derived antigens. Tumor neoantigens in the form of synthetic peptides or proteins, as well as resected tumors and RNA or DNA extracted from autologous tumor cells, are all potential antigen sources for personalized cancer vaccines.[3]

Immunizations against cancer: a categorization

We categorize existing cancer vaccines differently based on what is known about the immunogenic tumor antigen, which patients' tumors express that antigen, and how the antigens co-localize with professional antigen-presenting cells (APCs). Vaccine antigens can be either defined ahead of time

(known) or left unidentified (anonymous). As for the former, it can either be predefined shared antigens (expressed in many different patients' tumors) or individual antigens (exclusively determined for each patient). Vaccines containing anonymous antigens and APCs can colocalize ex vivo (in a lab) or in situ (at the tumor site).[4]

Mutation of malignant tumors' DNA

In recent years, it has become clear that genetically modifying tumor cells can result in vaccines with more precise biological effects.[5]

Definitions and a quick summary of mucosal vaccines

Given that cervical cancer is the fourth most common cancer in women, mucosal vaccines targeting the genital tract could be an effective tool in the fight against both sexually transmitted diseases and local tumors. Since the virus primarily infects the intestines, mucosal vaccination strategies are urgently needed. Worryingly, multidrug-resistant STDs are on the rise, but they may be defeated by mucosal vaccine strategies designed to prevent their spread.[6]

What we can learn from approved mucosal vaccines

Adjuvanted subunit and, more recently, viral vectored, RNA and DNA vaccines have largely replaced injectable whole-cell killed and attenuated vaccines. This is made easier by developments in antigen discovery, adjuvants, and delivery systems, all of which lessen the likelihood of severe adverse reactions. The situation with mucosal vaccines, however, is very different. Currently, there are nine mucosal vaccines on the market, eight for the oral route and one for intranasal use, and all of them are either live attenuated or whole-cell inactivated. The absence of proven mucosal adjuvants, the greater tolerability of orally administered whole-cell killed antigens, and the susceptibility of unprotected subunit antigens to degradation and clearance all contribute to this divergence of approaches.[6]

Immunization: What We Can Learn From Mucosal Tissues

Specific features of immune responses in the mucosa. Several factors about mucosal immune responses, such as the nature, duration, and distribution of induced effector and memory cells, play a role in the design of mucosal vaccines. Adaptive immune responses are mediated by effector sites like the lamina propria and epithelium. Inductive sites have different characteristics across species and mucosae.[7]

Therapeutic Response Models for the Assessment of Cancer Vaccines

When considering cancer vaccines as a therapeutic option, it is recommended that "patient response" be prioritized over "tumor response." These two phenomena are not necessarily interdependent on one another. Using the same response criterion across therapies, cancer types, and disease stages is a classic case of "paradigm paralysis," but standardization is essential for any clinical trial. The evaluation of passive therapeutic modalities, such as chemotherapeutic agents and radiation therapy, has been facilitated by the Response Evaluation Criteria in Solid Tumors (RECIST). However, the exclusive use of RECIST criteria as a clinical endpoint has been questioned by a number of Cooperative Groups with the advent of new targeted therapies such as cancer vaccines. One such instance is the testing of sorafenib in patients with metastatic renal cell carcinoma in clinical trials. Progression-free survival for sorafenib patients doubled from 12 to 24 weeks (P 0.0001) in a randomized, placebo-controlled phase III trial with 903 patients. At 3 months, the RECIST response rate was 10% for partial responses and 1% for complete responses. Another example is the testing of the drug imatinib for the treatment of patients with gastroesophageal stromal tumor. Likewise, in a clinical trial involving patients with metastatic renal cell carcinoma, the opposite is true. Three hundred and six people were split evenly between high- and low-dose interleukin (IL-2) therapy. A higher proportion of patients in the high-dose IL-2 treatment group experienced a response (21%) compared to the low-dose group (13%), as measured by RECIST

criteria (P = 0.048). Overall survival rates did not differ significantly between the two groups. These and other results show that the RECIST criteria do not always provide an accurate assessment of patients' clinical benefit (i.e., survival and quality of life)[7]

Human Studies of Vaccines

Previous studies uncovered 21 clinical trials demonstrating the clinical benefit of various cancer vaccines in various patient populations. This article will review the most up-to-date clinical data on the use of five different vaccines in the treatment of prostate cancer.

Why vaccines work so well against prostate cancer???? There are few treatment options after definitive primary therapy (surgery and/or radiation) because (a) it is a slow-growing tumor (b) recurrence is often diagnosed early in the disease state (c) there is a surrogate marker for disease prognosis and outcome [i.e. serum prostate-specific antigen (PSA) doubling time (d) there are few metastatic sites.[7]

Vaccination as a Potential Therapy for Non-Small Cell Lung Cancer[8]

When it comes to cancer deaths, lung cancer is currently the leading cause worldwide. More than 2 million people are diagnosed with lung cancer every year, and while the number of cases has decreased among smokers, it has increased among non-smokers and women. About 85 percent of all cases of lung cancer are non-small cell lung cancer (NSCLC), and most patients are diagnosed at a late stage. Over the past decade, the treatment of NSCLC has advanced greatly thanks to the introduction of targeted therapies and immunotherapy. Some patients have achieved responses with durations and survival rates previously unheard of in metastatic NSCLC treatment, making immune checkpoint inhibitors (ICIs) the cornerstone of advanced NSCLC treatment.

As a preventative measure against oral cancer

In a study conducted by Kitagawa and colleagues, In this research, mice with tumors made from syngeneic MBT-2 bladder cancer cells responded favorably to a combination of this oral vaccine and an anti-PD-1 antibody given after the vaccine. It has been documented that MBT-2 cells naturally produce WT1 protein. We used a tumor model that had not responded to anti-PD-1 treatment as a means of determining the best order in which to administer the two components of this combination therapy in order to address the significant unmet need for a treatment for anti-PD-1 antibody-resistant or poorly responsive tumors. We found that an oral vaccine alone significantly reduced tumor growth in this model, while a combination of an oral vaccine and continuous anti-PD-1 antibody treatment after the initial treatment with anti-PD-1 antibody had no effect. Treg cells, or regulatory T cells, were found in higher numbers in tumor tissues of combination-treated mice compared to oral vaccine-treated mice. ICIs are the gold standard for treating many types of advanced cancer, but they only produce a 20%-30% response rate when used alone. Pembrolizumab (anti-PD-1 antibody) monotherapy had an objective response rate (ORR) of 21.1% in patients with advanced urothelial cancer (including bladder cancer) in a phase III clinical trial. WT1 oral cancer vaccine, alone or in combination with anti-PD-1 antibody, may offer a novel treatment option for patients with advanced urothelial cancer.[9]

The Influence of Oral and Nasal HPV Vaccines on Nasal and Oral HPV Infection

The authors of this paper, K.J. Nielsen et al., searched PubMed and Embase extensively. Research on the effectiveness of HPV vaccines in preventing oral and oropharyngeal HPV infection was considered for inclusion. The relative prevention percentage (RPP), as well as a quality assessment and a risk of bias analysis, are presented in this review. Seven studies were included: two case-control studies, one longitudinal cohort study, one randomized community trial study, and five cross-sectional studies (48,777 participants). Cross-sectional studies had a mean RPP of 83.9% (66.6-97.8%), the included RCT had an RPP of 82.4%, and the longitudinal cohort study had an RPP of 83.0%. There were also two case-control studies that looked at antibody response in HPV

vaccine recipients. One hundred percent and 93.2% of vaccinated individuals, respectively, produced HPV-16 Immunoglobulin G (IgG) antibodies in oral fluids. There was a significant decrease in oral or oropharyngeal HPV infections among vaccinated study participants, regardless of study design or population composition. Not only that, but after vaccination, a sizable percentage of people had IgG antibodies in their saliva.[10]

Future challenges for vaccines exist.

The standard procedure for administering a unique neoepitope vaccine consists of several substeps. Cancer and healthy cell samples analyzed by NGS reveal whole exome and RNA sequencing data (the latter derived, in general, from circulating blood cells). The data from these paired samples is then compared using computational tools in order to detect cancer-related mutations and measure the expression levels of each mutated gene. Following this, mutations are prioritized according to the predicted binding affinity of the putative epitopes to the patient's HLA alleles and their expression, while also taking into account the clonality of each mutation. The most promising candidates are used to create new vaccines. Each patient is given a vaccine made from a combination of different predicted neo-epitopes. The results of the first-in-human trials show that full process integration and quality control are doable and consistent with standard procedures for clinical testing in a healthcare setting. For personalized cancer vaccines to advance, the following challenges must be overcome: The vaccine needs to be optimized for its immune-pharmacological purpose, production needs to be scaled up while still remaining affordable, and the best clinical indications and treatment protocols need to be determined.[11]

Cancer vaccines used in conjunction with existing therapies

Patients with metastatic cancer have an extraordinarily diverse set of regulatory/suppressive pathways, so eliciting a durable clinical response through vaccination is a significant achievement in and of itself. However, DC vaccines will need to be combined with other therapies that target different aspects of tumor development, such as tumor cell apoptosis, angiogenesis, tumor stroma, and inflammation, to overcome the tumor's suppressive environment and improve outcomes. Such protocols will incorporate a variety of interventions aimed at separate pathways. To inhibit tumor-associated cytokines that inhibit effector T cells directly or indirectly via macrophages and myeloid-derived suppressor cells, blocking antibodies or soluble receptors can be used. IL-10, IL-13, and TGF-b are all potential candidates. It is also possible to use blocking Abs to counteract immune-inhibitory signals in lymphocytes. Most notably, anti-CTLA-4 blocks the intrinsic T cell regulatory pathway, and anti-programmed death ligand blocks the extrinsic T cell inhibitory pathways driven by ligands expressed on tumors or DCs. On the other hand, anti-CD137, which is a ligand for 4-1BB, may be a good example of an agonistic antibody that promotes additional costimulation of effector T cells. We expect the development of clinical protocols that combine DC vaccines with individualized adjunct therapies, much like the way in which various tumors are currently treated with various combinations of cytostatic drugs and targeted therapies. Recent research suggests the immune system may mechanically contribute to the clinical efficacy of other cancer therapeutic modalities, such as: Herceptin Ab therapy, along with 1) radiation therapy and certain chemotherapeutic agents like anthracyclins. Combining cancer vaccines with these types of treatment may improve their efficacy.[12]

Conclusion

Finally, mRNA vaccines can be made rapidly and affordably. RNA-stimulated dendritic cells were the focus of the first mRNA-based cancer vaccine study, which was conducted in 1996. Pembrolizumab (anti-PD-1 antibody) monotherapy had an objective response rate (ORR) of 21.1% in patients with advanced urothelial cancer (including bladder cancer) in a phase III clinical trial. WT1 oral cancer vaccine, alone or in combination with anti-PD-1 antibody, may offer a novel treatment option for patients with advanced urothelial cancer. The authors of this paper, K.J. Nielsen et al., searched PubMed and Embase extensively. Research on the effectiveness of HPV vaccines in

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