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Review Article

Cancer vaccines: a newer front of immunotherapy

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ABSTRACT

Vaccines have been used as a promising instrument over the years to combat the dreadful communicable diseases. But now owing to epidemiological transition as the burden of non-communicable diseases has increased, efforts are now being made globally to use this weapon for non-communicable diseases like cancer. Cancer vaccines belong to a class of substances known as “biological response modifiers”. These work by stimulating or restoring the immune system’s ability to fight infections and disease. There are two broad types of cancer vaccines: Preventive (or prophylactic) vaccines and Treatment or therapeutic vaccines. Cancer treatment vaccines are made up of cancer cells, parts of cells or pure antigens. Sometimes a patient’s own immune cells are removed and exposed to these substances in the lab to create the vaccine. Cancer treatment vaccines differ from the vaccines that work against viruses. These vaccines try to get the immune system to mount an attack against cancer cells in the body. Instead of preventing disease, they are meant to get the immune system to attack a disease that already exists. Preventive vaccines are intended to prevent cancer from developing in healthy people. And in fact, many evidence-based studies have proven the decrease in morbidity and mortality in various cancers by usage of some of the vaccines like cervical cancer vaccine etc. The biggest challenges currently facing preventive anti-cancer vaccines are clinical, social, and economic in nature. This article is an effort to highlight the advances in various cancer vaccines, so done, to use them on preventive and therapeutic front.

Keywords: Immunotherapy, Preventive, Vaccines, Therapeutic

INTRODUCTION

Vaccines, most successful weapon against dreadful diseases some of which were greatest scourges of humankind have drastically decreased mortality over the time. Vaccine research has now opened up a second front by applying vaccination as a therapy for people already suffering from disease, which is not susceptible to a preventive approach. That is, yielding of an efficient tool against cancer.

More recently, the concept of vaccination has been developed into a potentially novel strategy to treat and prevent cancer formation, progression and spread.¹ Approximately 100 years ago, researchers attempted to stimulate a tumor specific, therapeutic immune response

to tumors by injecting patients with cells and extracts from their own tumors or tumors of the same type from different individuals.²

During the last decade, great efforts have been made to develop immunotherapeutic approaches for the treatment of malignant diseases as alternatives to traditional chemo and radiotherapy. A quintessential goal of immunotherapy in cancer is treatment with vaccines that elicit potent antitumor immune responses without side effects.³

What are cancer vaccines?

Cancer vaccines belong to a class of substances known as “biological response modifiers”. These work by

stimulating or restoring the immune system's ability to fight infections and disease.⁴ Cancer treatment vaccines are made up of cancer cells, parts of cells or pure antigens. Sometimes a patient's own immune cells are removed and exposed to these substances in the lab to create the vaccine.

Once the vaccine is ready, it's injected into the body to increase the immune response against cancer cells. Cancer treatment vaccines differ from the vaccines that work against viruses. These vaccines try to get the immune system to mount an attack against cancer cells in the body. Instead of preventing disease, they are meant to get the immune system to attack a disease that already exists. Vaccines are often combined with other substances or cells called adjuvants that help boost the immune response even further.

There are two broad types of cancer vaccines: Preventive (or prophylactic) vaccines and Treatment or therapeutic vaccines.⁵ Preventive vaccines are intended to prevent cancer from developing in healthy people. Currently, all of the licensed preventive anti-cancer vaccines used in clinical practice target virus-causing cancers (oncoviruses).

The most common one is the HPV vaccine (Gardasil) that was first licensed by the FDA in 2006 and recommended for use in females between the ages of 9 and 26 for the prevention of cervical cancer along with various other HPV-associated cancers (e.g., vaginal cancers, vulvar cancers, anal cancers, HPV-induced oral cancers, etc. Gardasil targets four specific subtypes of the HPV — 6, 11, 16 and 18 — of which HPV 16 and 18 cause about 70 percent of all cases of cervical cancer worldwide.

Treatment (or therapeutic) vaccines, are intended to treat an existing cancer by strengthening the body's natural immune response against the cancer. It is used to treat cancer after it has already appeared. There are two main types of such therapeutic vaccines: autologous vaccines and allogenic vaccines.^{6,7}

Treatment vaccines are a form of immunotherapy. Rapid advancements in the understanding of the immune system and its role in cancer have allowed for the development of therapeutic vaccines that utilize the host's own immune system to essentially prime it to specifically target, attack, and kill tumor cells. To date, the only therapeutic anti-cancer vaccine that has been licensed for use in clinical practice is sipuleucel-T (Provenge), which is used for the treatment of prostate cancer.⁸ It was first licensed by the U.S. Food and Drug Administration (FDA) in 2010 for use in the treatment of asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Unlike the HPV vaccine that relies primarily on generating an antibody response to prevent initial HPV infection,

sipuleucel-T (vaccine for prostate metastatic cancer) intends to treat the cancer.

The origin of concept of cancer vaccines

In 1891, Dr. William Coley, the "Father of Immunotherapy," made the first attempt to stimulate the immune system for improving a cancer patient's condition by intratumoral injections of inactivated *Streptococcus pyogenes* and *Serratia marcescens*.⁹ The idea came from the observation of spontaneous remissions of sarcomas in rare-cancer patients who had developed erysipelas.

Despite his reported effective responses in patients, his work was viewed with skepticism by the scientific community. Today, the field of immunology has developed into a highly sophisticated specialty, and the modern science of immunology has shown that Coley's principles were correct. Indeed, the bacillus calmetteguerin (BCG) that is one similar example as the Coley's Toxin, is still being used intravesically to treat superficial bladder cancer.

CURRENT SCENARIO

Viruses are the underlying cause in approximately 10 percent of all cases of cancer and are therefore an attractive therapeutic target for cancer prevention. Previous success with vaccines used to treat and prevent infectious diseases caused by viruses have provided a platform for identifying oncoviruses and utilizing the host immune system to effectively target and eliminate them. The biggest challenges currently facing preventive anti-cancer vaccines are clinical, social, and economic in nature. Debates are currently ongoing, and key decisions are still yet to be made with regard to how preventive anti-cancer vaccines can be delivered to a general population in an ethical and cost-effective manner.¹⁰ Over the past few years, a handful of anti-cancer vaccines have been licensed and approved for use in clinical practice, thus providing a breakthrough in the field. However, the path has not always been easy, with many hurdles that have had to be overcome in order to reach this point.

Nevertheless, with more anti-cancer vaccines currently in development, there is still hope that they can eventually become routine tools used in the treatment and prevention of cancer in the future. Of the handful of anti-cancer vaccines currently being used in clinical practice, perhaps the most famous of these is a prophylactic vaccine that targets a subset of the human papilloma virus (HPV†), which causes cervical cancer. For its discovery and development, Harald zur Hausen was awarded the 2008 Nobel Prize in Physiology and Medicine,¹¹ serving as a breakthrough moment and underlining the credibility of vaccination as a means of treating and preventing cancer.¹¹

Table 1: Currently used anticancer vaccines.

Anti-cancer vaccines	Effective against Cancers	Target group
Hepatitis vaccine (Engerix-B, Enivac B)	Hepatocellular cancer	Potent for all age groups, especially given to new-borns, after accidental exposure and chronic hepatic infections.
Human Papillomavirus (HPV) RQuadrivalent recombinant vaccine, (Types 6, 11, 16, 18) (Gardasil)	Cervical cancer Genital warts (condyloma acuminata) Cervical adenocarcinoma in situ (AIS) Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3 Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3 Vaginal intraepithelial neoplasia (vagin) grade 2 and grade 3 Cervical intraepithelial neoplasia (CIN) grade 1	Females 9 to 26 years of age for Prevention against cervical cancer caused by (HPV) Types 6, 11,16, and 18. Vaccination in boys and men 9 to 26years of age for the prevention of genital warts caused by HPV types 6 and 11 which do not cause malignancy.
Human Papillomavirus Bivalent Recombinant vaccine (Types 16 and 18) (Cervarix)	Cervical cancer Cervical intraepithelial neoplasia (CIN) grade 2 or worse Adenocarcinoma in situ, Cervical intraepithelial neoplasia (CIN) grade 1	Prevention of cervical cancer, in Females 10 to 25 years of age for prevention of cervical cancer especially caused by HPV type 16 and 18.
Sipuleucel-T (Provenge) (Approved in US)	Prostate cancer	For males with metastatic, symptomatic, minimally symptomatic, castrate-resistant (hormone refractory) prostate cancer.

HPV VACCINE

Persistent infections with high-risk HPV types can cause cervical cancer, anal cancer, oropharyngeal cancer, and vaginal, vulvar, and penile cancers. Three vaccines are approved by the US Food and Drug Administration (FDA) to prevent HPV infection. Hepatitis B virus (HBV) vaccines. Chronic HBV infection can lead to liver cancer. The FDA has approved multiple vaccines that protect against HBV infection. Two vaccines, Engerix-B and Recombivax HB, protect against HBV infection only. Both vaccines are approved for use in individuals of all ages. In April 2010, the FDA approved the first cancer treatment vaccine. This vaccine, sipuleucel-T (Provenge®), is approved for use in some men with metastatic prostate cancer.¹² Unlike some other cancer treatment vaccines, sipuleucel-T is customized to each patient. The vaccine is created by isolating immune system cells called dendritic cells, which are a type of antigen-presenting cell (APC), from a patient's blood through a procedure called leukapheresis (Table 1). Effective, safe and enduring cancer treatments constitute major challenges of medical sciences, with therapeutic cancer vaccines emerging as attractive approaches for provoking long-lasting protective antitumor immunity. Recent approval of the first therapeutic cancer vaccine will pave the way for developing innovative, next generation of vaccines with enhanced antitumor potency. Based on current data from clinical trials and the safety

profiles of therapeutic vaccines, they will most probably be used in the adjuvant or neoadjuvant setting for the treatment of patients with minimal residual disease or more indolent metastatic disease, or those patients with a high risk of recurrence.

A better understanding of host-tumor interactions and tumor immune escape mechanisms are required to develop effective cancer vaccines. Identification of unique tumor gene or protein products responsible for transformation of normal cells into tumor cells and promoting cancer progression will also uncover new potential targets for vaccine therapy. In addition, immune signatures will have to be established and exploited to define patient populations who will most likely respond to and benefit from vaccine therapies.¹³ Strategically combining vaccine strategies with other agents or approaches that synergistically enhance antitumor immunity and/or engage complementary antitumor responses should also lead to further improved clinical outcomes.

Promising anti-cancer vaccines currently in development

Vaccines are not yet a major type of treatment for cancer. Researchers have been trying to develop vaccines to fight cancer for decades, but this has proven to be harder than was first thought. As researchers have learned over the

years, the immune system is very complex. It has also become clear that cancer cells have different ways of eluding the immune system, which makes creating effective vaccines difficult.¹⁴ Researchers are using the knowledge gained in recent years to improve how they develop cancer vaccines.

They are studying the best way to give vaccines, looking to see if they work better when used alone or with other types of cancer treatments. For example, vaccines are now often given along with other substances (called adjuvants) that help boost the body's immune response, which might help the vaccines work better.¹⁵ (Table 2) Much recent attention has been given to the use of ex vivo-modified dendritic cells in tumor vaccine therapy; that is, dendritic cells¹⁶ modified in the laboratory.

While there are only a handful of anti-cancer vaccines currently available in clinical practice, over the years there have been many more that have been put through clinical trials.

One of the most advanced anti-cancer vaccines currently in development is the gp100 melanoma vaccine. Currently, two large ongoing phase III clinical trials (START and INSPIRE) are testing L-PLP 25 for the treatment of non-small cell lung cancer.¹⁷ One of the few types of anti-cancer vaccines currently in development for targeting TSAs is the antiidiotype vaccine. Cancer vaccines are now entering into a renaissance era, thanks to the series of clinical trials that are hopeful of yielding encouraging clinical outcomes for a plethora of cancers.

Table 2: Future cancer vaccines in development.

Cancer	Developmental research status of cancer vaccine ^{18,19}
Bladder cancer	One study is testing the effectiveness of a vaccine made from a virus, researchers modified to contain HER2 cells, which live on the surface of some bladder cancer tumors.
Brain tumors	Researchers are targeting at certain molecules on the surface of brain tumor cells for development of vaccine. Some focus on newly diagnosed brain cancer and on recurred one.
Breast cancer	Several studies are testing treatment vaccines for breast cancer, given alone or with other therapies. Other researchers are working to get prevention vaccines into clinical trials.
Cervical cancer	The FDA already approved cervical cancer prevention vaccines. Now work continues on treatment vaccines that help to treat the disease in its various stages.
Colorectal cancer	Researchers are creating treatment vaccines that encourage the body to attack cells with antigens thought to cause colorectal cancer. These antigens include carcinoembryonic antigen (CEA), MUC1, guanylyl cyclase C, and NYESO1.
Kidney cancer	Vaccines are being developed to treat kidney cancer at various stages and to avoid recurrence. Efforts are going to either make patient customized vaccine or from tumour surface proteins or blood vessel cells in the tumor
Leukemia	Treatment vaccines for various types of leukemia, such as acute myeloid leukemia and chronic lymphocytic leukemia are basically being focused on. Also, vaccines benefitting the other treatment modalities such as stem cell transplants are aimed at.
Lung cancer	Treatment vaccines in clinical trials target antigens- MAGE3, which is found in 42% of lung cancers and NYESO1, found in 30% of lung cancers. Others target antigens such as p53, survivin, and MUC1.
Melanoma	Researchers are testing several vaccines, given alone or with other therapies using destroyed melanoma cells.
Myeloma	Several clinical trials are in process studying vaccines with multiple myeloma near remission, smoldering myeloma or with autologous stem cell transplant.
Pancreatic cancer	Researchers are working on several treatment vaccines designed to boost the immune system's response to pancreatic cancer cells either alone or in combination with other therapy.
Prostate cancer	sipuleucel T is a vaccine to treat men with metastatic prostate cancer. Now researchers are trying to find if vaccine can help men with less advanced prostate cancer.

CONCLUSION

Cancer vaccines are not just a dream for the future, overall, the state of anti-cancer vaccines looks promising. With a few anti-cancer vaccines currently in clinical practice and several more currently in phase III clinical

trials, the future certainly looks bright for the once much-maligned concept. The question however still remains: Has a revolution truly begun or are anti-cancer vaccines just a one-hit wonder?

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