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Cancer vaccine

E.Rajeswari, M.Mounika, G.Ushakiran, N.Nagamalleswari, Y.A. Chowdary

**NRI college of pharmacy, Pothavarappadu, Agiripalli Mandal, Nunna, Vijayawada.*
***Address for correspondence: E.Rajeswari**

ABSTRACT

Cancer is an uncontrolled growth of cells that invade surrounding tissue replacing native cells resulting in disease and finally death. Mutation in genes that encode cell cycle proteins causes cancer. Cancer vaccination involves stimulation of the immune system, that promotes recognition and elimination of tumour cells. Proteins expressed on a target cell serve as antigens, which bind to receptors on T cells, leading to activation of the latter. Anticancer immunotherapy relies on effective targeting of antigens that can be recognized by high avidity T-cells. Success of cancer vaccine appears to be limited. Targeted vaccines become ineffective as the target mutates. Genetically engineered vaccines may prove to be ineffective as neutralizing antibodies may be produced. Adjuvants used for poorly immunogenic vaccines may prove to be toxic. Thus, the development of effective cancer vaccines require continued efforts, thoughtful clinical trials, and scientific progress which might induce long-term specific anticancer response with immune memory cells, and could contribute to effective and lasting elimination of malignant cells.

Keywords: Cancer, Cancer vaccine, Immunotherapy, Combination strategies, Autologous.

INTRODUCTION

Vaccines, also called vaccinations, are medicines that help the body to fight with disease. They can train the immune system to recognize and destroy harmful substances. Vaccination is the most effective way to prevent infection and severe outcomes caused by viruses. All medicines have side effects. But vaccines are among the safest, and the benefits of vaccinations far outweigh the risk of side effects. But a better approach is to try to balance the benefits of having a vaccine against the chances of harm. Younger children or babies may be a bit irritable or unwell, or have a slight temperature. Again, this usually goes away within 1 or 2 days. Most side effects from vaccination are mild and short-lived. In much rarer cases, some people have an allergic reaction soon after a vaccination. This is usually a rash or itching that affects part or all of the body. On very rare occasions, a severe allergic reaction may happen within a few minutes of the vaccination. This is called an anaphylactic reaction. It can lead to breathing difficulties and, in some cases, collapse. Remember that anaphylactic reactions are extremely rare (less than 1 in a million). Vaccination is different from giving medicine to an unwell child to make them better. The benefits of

vaccination are invisible. The idea is that child will not become ill with measles or end up in intensive care with meningitis. It may be tempting to say "no" to vaccination and "leave it to nature". But deciding not to vaccinate puts them at risk of catching a range of potentially serious, even fatal, diseases. In reality, having a vaccination is much safer than not having one. They're not 100% effective in every child, but they're the best defence against the epidemics that used to kill or permanently disable millions of children and adults.

Each cancer has a unique signature arising from specific mutations. These mutations are represented in epitopes which act as 'neo-antigens'. Using lymphocytes and tumour cells from a melanoma patient, a 'personalized vaccine study' demonstrated neo-antigens are associated with the long-term survival of melanoma patients. Indeed, patients whose tumours have a higher mutation rate often respond better to immunotherapy. Cancer vaccines have been investigated for more than 20 years for their efficacy in both preclinical models and in clinical trials in humans. There are clear advantages of whole-cell vaccination over those types of immunotherapy that target specific approach. Multiple and unknown antigens may be targeted to both the innate and adaptive immune system [1]. Current approaches prepare whole tumor cell vaccines, including traditional methods of freeze lysates, tumor cells treated with ultraviolet irradiation and RNA electroporation, along with more recent methods to increase tumor cell immunogenicity with replication incompetent herpes simplex virus [2] .

Vaccines are often very effective at inducing a strong T cell response but fail to achieve regression of an established tumour, due to the immunosuppressive tumour microenvironment. Combining vaccines with checkpoint inhibitors may improve the success rate. Combination therapy involving vaccines and checkpoint inhibitors is already in clinical trials, such as Neovax with Ipilimumab for treating renal cancer with Nivolumab for the treatment of melanoma, lung and bladder cancer.

A cancer vaccine **(**"autologous") is a vaccine that either treats existing cancer or prevents development of a cancer. Vaccines that treat existing cancer are known as *therapeutic* cancer vaccine. Cancerous cells routinely arise and are destroyed by the immune system; and that tumors form when the immune system fails to destroy them. Cancer treatment vaccines, also called therapeutic vaccines, are a type of immunotherapy. The vaccines work to boost the body's natural defenses to fight a cancer. The vaccines may: Prevent the cancer from coming back, Destroy any cancer cells still in the body after other treatments have ended and stop a tumor from growing or spreading. Developing cancer treatment vaccines that work is hard because:

- **Cancer cells suppress the immune system**: That is how the cancer is able to develop and grow in the first place. Researchers are using adjuvants in vaccines to try to fix this problem.
- **Cancer cells develop from a person's own healthy cells**: As a result, the cancer cells may not "look" harmful to the immune system. The immune system may ignore the cells instead of finding and destroying them.
- **Larger or more advanced tumors are hard to get rid of using only a vaccine**: This is one reason why doctors often give people cancer vaccines with other treatments.
- **People who are sick or older can have weak immune systems**: Their bodies may not be able to produce a strong immune response after vaccination.

That limits how well a vaccine works. Also, some cancer treatments may damage a person's immune system, limiting its ability to respond to a vaccine. Because of these reasons, some researchers think cancer treatment vaccines may work better for smaller tumors or early-stage cancers. Tumor cell vaccines may be:

- **Allogeneic:** vaccines made from melanoma tumor cells taken from individuals other than the patient.
- **Autologous:** vaccines made from melanoma antigens taken from a patient's own cancer cells.

A variety of cancer cells and cell fragments are used in tumor cell vaccines

- ✓ Whole tumor cells.
- ✓ Tumor lysates: fragments of destroyed tumor cells.

- ✓ Tumor oncolysates: an extract made from cancer cells infected with a strain of virus destructive to the cancer cells.
- ✓ **Apoptotic bodies**: fragments of cells that have died a natural death.
- ✓ **Transduced tumor cells**: cancer cells that have been altered through genetic engineering to include genetic material from cytokines, proteins that stimulate the activity of immune cells, including cytotoxic T cells [3]**.**

Immunoglobulin molecules contain highly specific, unique peptide sequences in their variable regions at the antigen-combining sites in the complementary-determining regions. These form the unique antigen recognition site of the Immunoglobulin protein and contain determinants that themselves can be recognized as antigens [4]. Results of the first clinical trial in patients with relapse follicular lymphoma have been encouraging, with evidence of both cellular immune responses and clinical responses in approximately 30% of patients [5].

As cancer cells have evolved various mechanisms for immune escape, combination therapies are needed to restore antitumour-immunity. Conventional therapies like chemotherapy and radiotherapy can be used to support antigen release by cancer cell death. Checkpoint inhibitors release the break on endogenous T cells by blocking the negative regulatory pathway used by tumours. They have shown efficacy on their own in various cancer types, however, less success was achieved in tumours devoid of infiltrating lymphocytes [6]. The lack of infiltrating T cells might be the result of a tumour suppressive microenvironment created by the cancer cells through the release of immunosuppressive cytokines, recruitment of regulatory T cells and myeloid-derived suppressor cells.

CANCER VACCINE TREATMENT

Most cancer treatment vaccines are only available through clinical trials, which are research studies involving volunteers. But in 2010, the FDA approved sipuleucel-T (Provenge) for men with metastatic prostate cancer. Metastatic means the cancer has spread from where it began to other parts of the body. Sipuleucel-T is customized for each person through a series of steps.

- ✓ First, white blood cells are removed from the person's blood. White blood cells help the body fight infections and diseases.
- ✓ Then the white blood cells are modified in a laboratory to recognize and target prostate cancer cells.
- ✓ Next the modified cells are put back into the person through a vein. This is similar to a blood transfusion. The modified cells teach the immune system to find and destroy prostate cancer cells.

Clinical trials are important for learning more about cancer vaccines. Researchers are testing vaccines for several types of cancers, including: Bladder cancer, Brain tumors, Breast cancer, cervical cancer, Kidney cancer, Leukemia, Lung cancer, Melanoma, Myeloma, Pancreatic cancer, Prostate cancer.

The so-called “cancer vaccine” currently being tested by researchers at the Stanford University School of Medicine doesn’t need to target specific tumor cells. Instead, it combines small pieces of DNA that amplify receptors on T-cells in the tumor necrosis factor (TNF) cytokine with an antibody that reactivates T-cells that have been suppressed by the cancer. Rather than being administered as a traditional vaccine to prevent the development of a disease, the Stanford team’s treatment is then injected directly into tumors. Once the T-cells within the tumor do their job, some then leave the previously cancerous cells in search of additional tumors to destroy. The team published their research in *Science Translational Findings* and is now moving from animal to human trials. Ronald Levy, MD, chief of oncology and professor at Stanford University and senior author of the report, said the treatment harnesses the power of the body’s own immune system to fight tumors.

Cancers often exist in a strange kind of limbo with regard to the immune system. Immune cells like T cells recognize the abnormal proteins often present on cancer cells and infiltrate to attack the tumor. However, as the tumor grows, it often devises ways to suppress the activity of the T cells.

Some of these tumor-specific, activated T cells then leave the original tumor to find and destroy other identical tumors throughout the body. The approach worked startlingly well in laboratory mice

with transplanted mouse lymphoma tumors in two sites on their bodies. Injecting one tumor site with the two agents caused the regression not just of the treated tumor, but also of the second, untreated tumor. In this way, 87 of 90 mice were cured of the cancer. Although the cancer recurred in three of the mice, the tumors again regressed after a second treatment. The researchers saw similar results in mice bearing breast, colon and melanoma tumors. Mice genetically engineered to spontaneously develop breast cancers in all 10 of their mammary pads also responded to the treatment. Treating the first tumor that arose often prevented the occurrence of future tumors and significantly increased the animals' life span, the researchers found. Vaccine also prevents recurrence.

LIMITATIONS

Today, most cancer vaccines are targeted. The limitations of targeted vaccines are very similar to the limitations of other targeted therapies in which not all patients' antigens are the same and tumor cells and their antigens mutate. Response of "targeted therapies" appear to be around 20 to 30 percent [7, 8]. In other words, when the targets change, the targeted vaccine becomes ineffective. Moreover, cancer cells used for the development of vaccines contain a high proportion of targets which are not cancer cell-specific, and an enrichment of cell surface material is needed to improve the effectiveness of cancer vaccines. Autologous vaccine therapy being very costly may also cause auto-reactivity and the subsequent development of an autoimmune disease. Patients treated with genetically engineered vaccines may produce neutralizing antibodies, which could cause subsequent therapies with the same product to become ineffective. The use of adjuvants in poorly immunogenic vaccines may increase immunogenicity of the vaccine, but may also cause increased toxicity . While cancer vaccination itself is a promising novel approach, its combination with additional therapies could produce much more synergistic effects [9].

There are ongoing studies to evaluate vaccine efficacy in men and adult women. Immunization with this vaccine holds promise for reducing the overall burden of clinical diseases [10].

CONCLUSION

This, however, is not the only reason why the researchers were excited. In fact, the experimental vaccine has another positive effect — namely, protecting the body against tumor recurrence. Last but not least, recent studies suggest that the immune system is likely to contribute mechanistically to the clinical efficacy of other therapeutic modalities in cancer, including the following: 1) radiotherapy and some chemotherapeutic agents, for example, anthracyclins [11], as well as 2) Antibody therapy such as Herceptin [12]. Thus, cancer vaccines might be more efficient, when combined with such treatment modalities.

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