



Cancer Vaccine

Nandini Mukherjee

Professor, Dept. of Medicine, R. G. Kar Medical College, Kolkata 700 004.

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INTRODUCTION

Vaccine therapy in malignancy is the most promising form of immunotherapy. The significant difference of cancer vaccine from other conventional vaccine used in infective diseases that it has got definite role in therapy rather than only prevention. Possibly use of BCG vaccine is the oldest form of vaccine therapy in malignancy. This was used to augment helper T-cell response against tumor cell antigen. Thereafter, invention of different tumor antigens involved in carcinogenesis and evolution of newer and newer methods in biotechnology help us to institute many different forms of vaccine therapy in malignancy.

PLACE OF VACCINE IN IMMUNOTHERAPY

1. Active:

Refers to immunization of tumor host with materials designed to elicit an immune reaction capable of eliminating or retarding tumor growth.

It may be:

- Non-specific e.g. immune adjuvants like attenuated bacteria e.g. BCG or *C. parvum* and chemical agent e.g. levamisole
- Specific e.g. tumor vaccine.

2. Passive

Involves the transfer of tumor bearing host of previously sensitized immunologic reagents that have ability to

accelerate anti-tumor responses directly or indirectly. It may be:

- Direct e.g. monoclonal antibodies
- Indirect e.g. removal or blocking of growth promoting factor of the molecule or inhibition of angiogenic factor.

3. Adaptive

Involves transfer of specially processed cells e.g. lymphocytes and macrophages e.g. lymphocyte-activated killer cells or tumor-infiltrating lymphocytes.¹

WHY BODY'S NATURAL IMMUNE RESPONSE DOES NOT REJECT THE TUMOR CELLS?

Tumor antigens are weakly immunogenic. They are not truly foreign, but physiological molecules altered in subtle way or becoming more abundant. Tumor cells act as poor antigen presenting cells (APC), as they lack adequate MHC molecules on the surface. So the cells are not easily recognized by the immune system.

Tumor cells secrete suppressor cytokines so that T- cells are unable to respond to antigen.

Tumor cells may have developed ways to escape which include shedding of tumor antigen and reducing number of molecules or receptors that activate T- cells or immune system.

Table I: Phase III clinical trials with some newly developed vaccines

Type of cancer	Breast (Metastatic CA)	Follicular B-cell NHL(First complete remission)	Follicular B-cell NHL (Stage III&IV- After completing chemotherapy)	Kidney (Surgically removed non-metastatic renal cell carcinoma)	Lung (small cell CA)
Vaccine name	Theoratope	Not named	GTOP 99	Oncophage	BEC2
Place of trial/Year	EMD Pharma Merck/2001	National Cancer Institute/2000	Genitope Corporation/ 2000	Antigenics/ 2000	EORTC/ 1998
Components	Synthetic sialyl Tn fused to KLH	Idiotypic proteins chemically attached to KLH GM-CSF	KLH GM-CSF (Sargramostin) attached to antigen	Heat shock protein peptide complex (gp96)	GD3 Ganglioside found on the tumor incorporated into mouse antibody engineered to resemble human protein

Table 2 : Phase III Clinical Trials with some Newly Developed Vaccines

Type of cancer	Melanoma (Primary, stageII)	Melanoma (Locally advanced)
Name of vaccine	Not named	Not named
Place of trial/Year	EORTC/2002	National Cancer Institute
Components	GM2 conjugated to adjuvant KLH Q S21	A combination of three specific antigens (tyrosinase, gp100, MART I)
Type of cancer	Multiple Myeloma	Prostatic (Metastatic)
Name of vaccine	Not named	Not named
Place of trial/Year	National Cancer Institute	Northwest Biotherapeutics/2002
Components	Myeloma immunoglobulin plus idiotype protein attached to KLH GM-CSF	PMNs from patient's blood plus IL-4& GM-CSF stimulated by PSA and treated with adjuvant BCG.

HOW THE DIFFICULTIES CAN BE OVERCOME?

- To make the cells more immunogenic:
 - by incorporating specialised leucocytes called dendritic cells into the system. These cells act as APCs by taking into the tumor antigen and presenting it to the T- cells, which are then stimulated to multiply and attack the tumor cells.
 - by placing the gene for the tumor antigen into a harmless viral vector which acts as a vehicle to deliver the gene to the targeted cell.
 - by adding genes for one or more immuno-stimulatory molecules into the vector along with the gene for tumor antigen.²
- Another technique is to attach a decoy substance to the antigen that is definitely foreign and that can stimulate the immune system. They are weakened protein or bacteria and trick an attack both on this substance as well as the tumor cells. These are called adjuvants which may be
 - chemical polymers e.g. muramyl peptide analog, lipid analog or saponin,
 - attenuated bacteria e.g. BCG, *C. parvum*. Adjuvants act as depot of antigen by slow release and phagocytosis and activate complement or cellular immunity.
- The most recent idea is to find out the antigen that is not present in normal adult cells. One of such unique cancer antigen is oncofetal antigen that is developed during embryogenesis but dies down in early neonatal life.

TYPES OF CANCER VACCINE

1. Prophylactic Vaccine:

The only FDA approved vaccine is the vaccine against hepatitis B virus that is known to promote hepatic carcinoma.

The other preventive vaccine is the vaccine against Papilloma virus which is shown to produce cervical carcinoma.

2. Therapeutic Vaccine:

- Cancer-specific:** Some cancer vaccines treat only specific types of cancer, because they target antigens found on specific cancers e.g. prostate-specific antigen in prostate cancer.
- Non-specific vaccines:** Vaccines that target antigens, found on many different kinds of cancer cells, are used to treat multiple cancers. The effectiveness varies with amount of antigens present in different cancers.
- Autologous tumor vaccine:** Patient's own tumor cells are used to generate a vaccine intended to stimulate a strong immune response. Such therapy is tumor-specific also. They do not attack the normal cells.
- Allogenic tumor vaccine:** The vaccine prepared from tumors of multiple patients is used to treat a particular patient.

Scientists are in constant search of a universal cancer vaccine, which is still far from reality.

ANTIGENS EXPLOITED FOR DEVELOPMENT OF VACCINE

- Prostate-Specific Antigen:** Found in blood or cancer cells of prostatic carcinoma. Normally it is present in minute amount in blood in male but increases manifold in prostatic carcinoma.
- Sialyl Tn:** Small carbohydrate molecule (oligosaccharide) that mimics the mucin molecule is present on cell surface of a number of malignancies, especially on poorly differentiated cells of myeloid series.³
- Heat Shock Proteins (gp96):** These are produced in response to heat, low sugar levels and other stress signals. Besides protecting against stress these molecules are involved in proper processing, folding, and assembling of proteins within the cells. The human vaccine consists of heat shock protein and associated peptide complexes isolated from a patient's tumor. This vaccine is under investigation of several cancers including liver, skin, colon, lung, lymphoma, and prostate cancer.
- Ganglioside molecules (GH2,GD2,GD3):** They are complex lipopolysaccharide molecules in which gangliosides are incorporated into the outside membrane of the cell. They make the cell more easily recognizable by the antibodies. GM2 is expressed on cell surface of many human cancers and GD2, GD3 contain carbohydrate moieties expressed by human cancer cells.
- Oncofetal antigens:**
 - Carcinoembryonic antigen:** Thought to be released by tumor cells into the blood stream in colorectal, breast, lung, pancreatic carcinoma and found to mount T-cell response.
 - Hanganitzu- Deicher antigen:** Found on red cells and lymphocytes in non-Hodgkin lymphoma. This is under investigation.⁴
 - Oligosaccharides:** Found on immature cells of myeloid series.

6. **Mart-I:** It is an antigen expressed by melanocytes and is a specific marker of melanoma. It is recognized by T-cells and is more abundant in melanoma cells. Tyrosinase is a key enzyme involved in initial stages of melanin production. It is also a specific marker for melanoma and more abundant in melanoma cells.

By exploiting these two antigens the vaccine for melanoma is prepared.

FIVE CATEGORIES OF CANCER VACCINE

Cancer vaccines are of five categories according to their components and biotechnological methods for their preparation.

1. **Antigen vaccines:** The antigens are produced continuously even when the cells are killed and able to stimulate the immune system. By injecting these killed cells or antigens into cancerous area, the immune system will produce an increased amount of cytotoxic T-cells or antibodies to attack cancer cells that carry the specific antigen. Multiple antigens can be used to vary the immune response. Whole cell vaccine is being increasingly used now, as it is a better immunostimulant. Different adjuvants are incorporated into the antigen vaccine to increase its immunogenicity.
2. **Anti-idiotypic Vaccines:** Antibodies produced by certain cancer cells (B-cell lymphoma and myeloma) called idiotype antibodies are unique in each patient and can be used to trigger an immune response just like an antigen vaccine.⁵
3. **Dendritic cell Vaccines:** Dendritic cells break the cancer antigen into smaller pieces on the cancer cell surfaces and work to programme the T-cells. Scientists extract some of the patient's dendritic cells by the process of leukapheresis. These cells, stimulated to multiply, and exposed to antigen extracted from patient's cancer cells, are injected into the patient to activate the immune system and to kill the cancer cells.
4. **DNA vaccine:** Bits of DNA from the patient's cancer cells, when injected into the patient, instruct other cells to produce antigens continuously, the antigen thus increased, forces the immune system to respond by producing more T-cells.⁶
5. **Viral vectors and DNA vaccine:** Nucleic acid sequence of the tumor antigen is incorporated into a harmless virus that acts as a vehicle to deliver the genetic material to the targeted cells to stimulate the immune response. Alternatively these are incorporated into antigen presenting cells.

DIFFERENT ADJUVANTS USED IN VACCINE

1. **Keyhole Limpet Hemocyanin (KLH):** It is a protein manufactured by a shelled sea creature that causes immune response and acts as a carrier of tumor cell antigen. KLH provides additional recognition sites for immune cells known as cytotoxic T-lymphocytes.
2. **Bacillus Calmette Guairin (BCG):** It is an inactivated tuberculosis bacterium routinely used to vaccinate against TB. It is shown to mount immune response to cancer cells but the mechanism is unknown.
3. **Interleukin-2 (IL-2):** It is a protein made by body's immune system that may boost cancer killing ability of natural killer cells, though this type of vaccine is not effective in relapse.

4. **Granulocyte Macrophage Colony stimulating factor:** It is a protein that stimulates proliferation of APCs and thereby used as adjuvant.
5. **QS21:** It is a plant extract, which when added to some vaccines, improves the immune response.
6. **Montanide ISA-S1:** It is oil-based liquid intended to boost an immune response.

Some recent biotechnology to produce vaccine with superior efficacy

1. The efficacy of DNA loaded with attenuated *S. typhimurium* and dendritic cells loaded with beta galactosidase protein has been tested. The superiority of these two types of vaccine is suggested as due to two different reasons. The former is due to strong activation of both CD8 and CTL cells by transformed *Salmonella*. The latter is due to sustained activation of non-adaptive defense mechanism by stimulation of thymocytes.⁷
2. Dendritic cells are potent antigen presenting cells, but their phenotype is relatively unstable so immunostimulatory capacity is varied. To obviate this difficulty costimulatory cytokine genes are transplanted into them to improve antitumor activity.⁸
3. Surface bound IgE plays a central role in antiparasitic immunity. To exploit this immune mechanism in tumor prevention and control, preparation of monoclonal IgE of irrelevant specificity, bridging onto tumor cells has been made. This is effected either by systemic administration of IgE to tumor-bearing mice or preloading of tumor cells with IgE before inoculation. IgE targeted on tumor cells not only possesses a curative potential but also confers long-term antitumor activity.⁹
4. Efficient loading of MHC class II molecules with a T helper epitope of choice can be achieved through genetic exchange with a sequence encoding helper peptide. This cellular vaccine provides peptide specific helper T cells. This is superior to cells loaded with synthetic T helper peptide.¹⁰

HOW DOES CANCER VACCINE WORK?

1. It makes the tumor cells more immunogenic and better target for immune system.
2. It overcomes the effect of inhibitory cytokines secreted by tumor cells.
3. It increases the amount of antigen presented to immunoreactive cells.
4. It augments the activity of T cells and natural killer cells.

ADMINISTRATION AND SIDE EFFECTS OF CANCER VACCINE

1. Cancer vaccine is usually liquid which is injected under the skin.
2. The frequency of administration depends on the type of cancer to be treated and type of type of vaccine used.
3. The possible side effects are a skin reaction at the site of injection, a skin rash and a mild flu-like syndrome. These are easily amenable to treatment.

4. Some cancer vaccines may produce more specific symptoms e.g. enlargement of lymph glands, which should be told before starting the treatment.
5. Vaccine therapy, unlike chemotherapy, is nontoxic to normal tissues and has a long half-life and need not be repeated.

CONCLUSION

Vaccine therapy is the most prospective form of therapy in malignancy. It is just thrilling to imagine if cancer can ever be eradicated like small pox or polio. Scientists are designing how larger and larger human trials can be conducted. While they achieve some success with someone or the other, it is still too early to predict when an ideal cancer vaccine will be developed.

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