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Review Article

CANCER VACCINE EMERGING TREATMENT: PRESENT AND FUTURE PROSPECTIVES

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ABSTRACT

Cancer is one of the main health problems of mankind. Treatment of cancer can include chemotherapy, surgery, hormone therapy, radiation therapy and biological therapy. A Cancer vaccine shows potential contrivance in the hands of the clinical oncologist. Cancer vaccine therapy is the augmented understanding of mechanisms involved in an antigen- specific T-cell and antibody-mediated or B-cell response. More recently, cancer vaccines targeting well characterized tumor-associated antigens, i.e. molecules selectively or preferentially expressed by cancer cells but not by normal cells have been designed and tested in humans. Outcome obtained as of today with these second-generation vaccines suggest that they are safe and that they can elicit humoral and cellular responses against tumor-specific antigens, without inducing unacceptable experimental signs of autoimmunity. This review summarizes the current knowledge of tumor immunology and types of vaccine. Recently used various vaccine delivery techniques like use of different route and physical or chemical delivery are used system with the objective to induce immunity next to tumor-associated antigens.

Keywords: Cancer vaccines, Immunotherapy; Tumor-associated antigens, Immunoadjuvants (IA)

INTRODUCTION

Cancer is one of the main health problems of mankind. In spite of extensive research being conducted over many years, effective cures have been developed only for some forms of cancer, so that the hazard is not substantially reduced. The search for new and better therapies is a constant challenge to the biological and medical sciences. Cancer is a leading reason of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) in 2008. The major types of cancer with relative their life threaten provided by WHO is as, Breast (460 000 deaths), Colorectal (610 000 deaths), Liver (700 000 deaths), Stomach (740 000 deaths), Lung (1.4 million deaths).the major death due cancer was from the developing countries i.e.70%. And it is projected that it will raise over 11 million in 2030. [1]

There are several techniques that are used in the diagnosis and treatment of cancer, this includes:

- Chemotherapy
- Surgery
- Immunotherapy
- Hormone therapy
- Radiation therapy

From long time and majorly used technique for treatment of cancer patients is Surgery. According to the American Cancer Society out of people diagnosed with cancer sixty percent will undergo surgery, before metastasis of cancer cell it have the anther option is to remove entire tumor. But it is not the stand alone option it usually combination of radiation or chemotherapy. [2, 3]

In radiation therapy, the particular organ of the body will expose various radiations to reduce reproducing cancer cells results in various side effects like including dryness, fatigue and nausea, peeling of skin and vomiting. Radiation therapy leads to shrinkage of cancer cell and also used to prevent reoccurrence of cancer cells after surgery. Chemotherapy is treatment of cancer by the use of various medicines it is the most effective method in case of failure of other method or used in combination with other therapies. Similar to radiation therapy it also is used to cure, prevent spread and modify the symptoms. The most recently used treatment are hormonal and immunotherapy. These involves the change in or controls the balance hormonal level for cancer treatment, it also includes the surgical removal of affected hormonal glands. Although these treatments are only life extending for many patients, those are rarely curative for spread cancers in body.[4]

Cancer vaccines are agents which are responsible for modification of biological responses. These act by stimulating or restoring the immune response to fight against the infection or disease medicines that belong to a class of substances known as biological response modifiers. The basic of biological response modifiers is they act by stimulating or restoring immune system against infections or disease. [5]

Two developments have led to a resurgence of interest in developing new cancer vaccines. These are:

1. The ability to transfect cell lines with a variety of immunomodulatory enhancing genes such as cytokines and co-stimulatory factors.
2. The identification of a number of new tumour specific associated antigens which can be purified for therapeutic use.

Immunotherapy may be classified into several types, including

1) Active Immunotherapy - Specific stimulation of patient's immune system with vaccines, and/or nonspecific stimulation using adjuvants;
2) Passive Immunotherapy - Treatment with exogenously produced antibodies;
3) Adoptive Immunotherapy - Transfer of lymphocytes and/or cytokines;
4) Restorative - Designed to restore deficiencies in the patient's immune response; and
5) Cytomodulatory - Meant to enhance the expression of major histocompatibility complex (MHC) molecules on the surface of the tumor cells. [6]

Tumor Immunology

The two major components of the immune system include the humoral (antibody-mediated or B-cell) and cellular (T cell) immune system. It is believed that cell-mediated immunity provides the primary immune response in tumors. [7, 8]

There are two types of responses

- Innate and
- Adaptive immunity

Innate immunity allows the body to distinguish between normal or "self," and "non- self" (e.g. infection, malignancies, or transplanted organs). With innate immunity, a nonspecific immune effect transpires, which harnesses macro- phages and natural killer cells to eliminate the offending organism. Innate immunity is not antigen specific and has no immunologic memory.

Innate and adaptive immunity play a part in the immune response to tumors. Although many cell types are involved in antitumor activity, T cells are the most important in developing antitumor activity. Adaptive immunity is antigen dependent and starts when the

phagocytized antigen is presented to B lymphocytes or T lymphocytes. [1, 3, 8]

Major Histocompatibility Complex

Antigens recognized by the immune system are presented by two types of MHC molecules, viz

MHC class I
MHC class II.

MHCs are the transmembrane glycoproteins displayed on cell surface acquiring intracellular peptide antigens having four domains on its surface such as peptide-binding domain, an immunoglobulin-like domain, a transmembrane region and a cytoplasmic tail. In humans, the HLA-A, -B, and -C molecules belongs to MHC class I molecules and HLA-D molecules belongs to MHC class II molecules.MHC class I molecules have 8 to 11-amino acid–long peptides derived from the digestion of intracellular proteins by the proteasome complex. CD8 T cells surface display the complex. Professional antigen-presenting cells (APCs) have the MHC class II on its surface and have more restricted distribution like dendritic cells, macrophages, and activated B cells. The MHC classes II consist of longer peptides with 10 to 34 amino acids, and derived from exogenous proteins endocytosed into end some lysosome compartments. [9]

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Tumor Antigens

The rational design of a cancer vaccine depends upon the identification of tumour antigens that can be targeted by the immune system, as well as strategies' in antigen presentation to overcome tolerance. Tumour antigen can be classified into various categories based on their pattern of expression:

a) Unique tumour antigen expressed exclusively in the tumour from which they were identified

b) Shared tumour specific antigen which are expressed in many tumours but not in normal adult tissues and

c) Tumour associated differentiation antigens (TADA). That is, antigens normally expressed in the tissue from which the tumour has arisen, but inappropriately expressed by the tumour. Furthermore, oncogens and products, tumour suppressor gene products, and viral antigens in virus- associated tumours are also candidate for targeting by the immune system. [10]

Table 1:Tumour Antigens [11, 26]

Unique tumor-specific antigens Mutant p21/ras,Immunoglobulin idiotype β-catenin,Mutant p53,CDK4
Shared tumor antigens : MAGE
Tumour-specific antigens (high affinity, no tolerance) 1. Viral antigens associated with tumour pathogenesis: EBV – lymphoma, nasopharyngeal cancer HPV - Cervix, Anal (several other sites suspected) HBV/HCC – Hepatoma (liver cancer) 2. Mutation antigens Specific tumour and no other tissues: ras, p53 bcr/abl, CDK-4, Caspase8
Tumour-associated antigens (wide spectrum of affinity and tolerance) 1. Cancer testes (CT) antigens, restricted to: Primitive germs cells of the testes and following activation of expression in a number of tumours MAGE-1–3, GAGE, BAGE, RAGE, PAGE, NY-ESO-1 2. Differentiation antigens: normal tissues with altered expression on tumour cells MART-1/Melay A, gp100, tyrosinase, TRP-1/2 GM2 ganglioside, HER-2/neu, CEA, MUC

Types of Vaccines

There are major categories that cancer vaccines fit into:

In Vivo APC-Based Vaccines

Intratumoral bacillus Calmette-Guerin (BCG)

The BCG vaccine has been used to induce anti-cancer immune responses nearly as long as it has been used against TB. In randomized studies it appears to have a small but not significant difference in the treatment of leukaemia, melanoma and prostate cancer [11] the earliest form cellular immunotherapy tested in cancer is Intratumoral injection of the BCG. Ideal for the attraction of APCs is the basis for immunology. To generate an inflammatory process by BCG, which is called danger environment by accepting the tumor antigens released by the tumor cells, damaged due to the bacterial infection and cross-present them. Many studies using cells also use BCG as an adjuvant. [12]

Intratumoral HLA-B7

In negative subjects the intratumoral injection of the alloantigen HLA-B7 leads to an innate reaction to the foreign HLA molecule. Amongst other inflammatory cells, recognition of alloantigenic permitted APCs in case of intramuscular injection of BCG will accepting tumor antigens released by the HLA-B7–transfected cells and cross-present those to cytotoxic effectors cells.

Whole-cell tumor vaccines

From decades Whole-cell tumor vaccines have undergone clinical investigation. Whole tumor cell vaccines are either irradiated live cell vaccines or tumor lysates based on autologous, allogeneic or mixed cancer cells to optimize liberation of their antigens. These Vaccines are jointly injected with potent immunologic adjutants or haptens (diphtheria toxin, BCG, dinitrophenyl, keyhole limpet hemocyanin, and virus) or both all the way through the rationale of presenting the tumor antigens in an inflammatory event to attract host APCs. [12, 13] First generation of whole tumor cell vaccines was composed of irradiated (50–150 Gy) autologous or allogeneic (one or more cell lines) cells or cell lysates admixed with adjuvant(s) such as BCG (Bacillus Calmette-Guérin), CpG (Cytosine–Phosphate–Guanine), aluminium etc. Second generation – gene modified whole tumor cell vaccines – consisted of autologous or allogeneic cells modified with gene(s) encoding cytokines, designer cytokines, growth factors, HLA (Human Leukocyte Antigen), costimulatory molecules etc. [13]Gene modified tumor vaccines are characteristically composed of autologous tumor cells tightly transferred with an immunostimulatory gene.

Heat shock proteins

Non-Hodgkin lymphoma (NHL) contributes 4% of new cancer in united state per year. It is predicted that 58,870 people will be diagnosed with NHL in 2006; approximately 40% will have a form of the disease with an indolent histology. Although several new treatments for patients with indolent lymphoma have been introduced, still more effective, novel, and safe treatments are needed to further prolong remission and improve survival of patients with indolent lymphoma. [1]

A component of HSPPC, heat shock protein (HSP) functions as a peptide chaperone, stabilizing and delivering peptides. Because HSPs can carry the ''fingerprints'' of antigenic epitopes for any type of tumor, HSPPC can exert its efficacy as a vaccine, bypassing the need to identify a specific peptide in order to induce immunity. Immune response induced by an HSP-based vaccine begins with antigen-presenting cells taking up antigenic epitopes with HSP and presenting the epitopes on major histcompatibility complex (MHC) class I molecules. [14]

Peptide-based vaccine

In early 1990, after cloning of the first human tumor-associated antigen (TAA) gene, for cancer management peptide vaccine shows the prospective role. Current developments in the peptide-based vaccines have shown the new strategies necessary for successful anticancer immunization. The interesting opportunity offered by

long peptide representing TAA epitopes which induce robust antitumor activity. As the large molecule these peptide binds to major histocompatibility complex (MHC) class I molecule, as these are 8 to 10 amino acid long. [15]

Recent clinical trials using peptide-based vaccines in renal cell carcinoma patients: CA-IX derived peptide, HLA-A 2402-restricted 9-mer WT1 peptide, Heat killed M. vaccae (SRL172), Heat killed M. vaccae (SRL172), IL-2 alone, IL-2 + SRL172 [28]

Naked DNA

DNA vaccines are disease-specific antigens are promoter elements which are active in mammalian cells. They also contain a transcriptional terminator to terminate transcription in mammalian cells and a selectable marker to facilitate production of the plasmids in transformed bacterial cells. The two-fold, action of plasmid DNA vaccines is, Firstly plasmid encode antigen and produces in host cell, cross priming is either in professional antigen presenting cells (APCs) foremost to direct priming of immune responses or in non-professional cells because if the antigen can be transferred to APCs. Secondly, because DNA plasmids are derived from bacteria they stimulate the innate immune system by interacting with Toll-like receptor. This non-specific immune response augments the antigen-specific immune response. [16]

The generation of immune responses may occur due to Intramuscular injection of naked DNA sequences which also results in gene expression. Antigen gene present in DNA plasmid has constitutive activity, which is injected into the skin using a helium gas gene gun in conjugation with gold particles. [9]DNA vaccines have several potential advantages over peptide and recombinant viral vaccines. DNA vaccines are simpler and cheaper to produce. [6]

Viral vectors

Viral vectors are an attractive choice of antigen delivery system for cancer immunotherapy since they mimic a natural infection and provide potent danger signals. Numerous viral vector systems have been developed since the first recombinant vaccinia viruses were constructed more than 20 years ago. [9] In 1982, vaccinia virus was described as the first recombinant viral vector system. Insertion of tumor antigen DNA sequences into attenuated pox viruses prevents it's replication in mammalian hosts (like modified vaccinia Ankara, fowlpox, or canarypox). In 1982, vaccinia virus was described as the first recombinant viral vector system. [25]

A large number of different recombinant viral vector systems have been evaluated as cancer vaccines in preclinical models. Of those only a small proportion has been evaluated in clinical studies. The majority of clinical studies to date have evaluated recombinant poxvirus vectors and to a much lesser extent recombinant adenoviruses. The unequal distribution of the use of these two types of virus in clinical studies is mainly historic. The immunogenicity of these vectors has been established in numerous preclinical models and human safety data is available. Most importantly, recombinant poxviruses and adenoviruses are genetically stable and GMP production has been established. Recombinant adenovirus has been developed mainly as a gene therapy vector and a recombinant adenovirus vector expressing the wild type p53 gene has been licensed for gen therapy of squamous cell head and neck cancer in 2003 in China. [17]

The prime-boost strategy

Effective methods to generate immune responses of tumor antigens are the prime boost strategies. The naked DNA and viral vector are chronologically administered which results in synergistic immune activation. [9]

Bacterial vectors

Bacteria such as Salmonella and Listeria are introduced in tumor antigen segment, resulting in protective immunity in animal models. These vectors have advantages of oral route for immunization and bacterial product creating strong inflammatory milieu leading to the attraction of APCs, and a favored Th1 cytokine polarizing outline stimulated by firm bacteria such as Listeria.

Ex Vivo APC-Based Vaccines

Dendritic cells

Dendritic cells are the most effective antigen-presenting cells; one of the primary goals of vaccine therapy is to target these cells Dendritic cells express Fc receptors that will bind anti-idiotypic antibodies, allowing the antigen to be presented in the context o class I and II MHC molecules, eliciting both cytotoxic and help T-cell responses. [18]

The explanation of culture measures to generate great quantities of dendritic cells ex vivo early from hematopoietic precursor or peripheral blood monocytes have allowed extensive testing in potential preclinical models and pilot clinical trials. Different antigen loading actions are used for dendritic cell antigen presentation. Synthetic HLA-binding peptide epitopes or the absolute DNA series in a viral vector can be used to load the dendritic cell vaccines for well-identified antigens. [31]

Clinical trials of DC vaccination have been made possible by the development of methods for obtaining large numbers of human DC. Two general approaches have been employed: i) the purification of immature DC precursors from peripheral blood and ii) the in vitro differentiation of DC from CD34+ progenitors or blood monocytes. [24]

Generally the sub types which used in clinical trials are: Mature monocyte-derived DC (mat-modc), immature monocyte-derived DC (imm-modc) and Density-enriched DC. [34]

Exosomes

Exosomes are small vesicles and are produced my most/all cell types, and have a molecular phenotype which largely reflects that of the parent cell. Exosomes produced by cancer cells are compositionally different from those produced by non-cancer cells, in that they express tumour-associated antigens. Exosomes may be an efficient mode for delivering these antigens to dendritic cells, and as such may be useful as cancer vaccines. Because cancer-exosomes are very complex, we have also been investigating the possible inhibition of correct immune function(s) driven by exosomes,and our research is helping to define exosomes as a major mechanism of cancer immune evasion. We are currently focussing on exosomes isolated from prostate cancer,and pleural malignant mesothelioma.

Non–T-Cell–Directed Cancer Vaccines

Surface receptors Monoclonal antibodies are effective against tumor e.g. trastuzumab or rituximab, which have complex mechanisms of action. It includes cell mediated cytotoxicity which is stimulated by antibody. Antibodies can target the tumour antigen like tumour growth factor and improve the response against cancer; trntuzumab was the first antibody than targets the HER2/neu protein which approved for treatment of metastatic breast cancer. There are several vaccines which are under clinical trial. Naturally produced Interleukin-2 (IL-2) and Interferon produced by body can also use to stimulate immune responses.

Immunoadjuvants (Ia)

The goal of cancer vaccines is to mount an effective T-cell reaction against the tumor. As mentioned previously, tumor cells do not produce the necessary proinflammatory cytokines and chemokines, or warning signals, necessary for the immune system to mount a sufficient response. Cytokines are protein hormone messengers having key role in mediating T-cell activation and proliferation. Chemokines are a group of cytokines that act as chemoattractants. They are produced locally by tissues, usually when a pathogen is present, and act on leukocytes to induce immune cell activation. By adding cytokines, chemokines, or other costimulatory molecules to vaccines, warning signals can be generated. These molecules are known as Immunoadjuvants. [4]

Generally, IAs are believed to activate innate immunity mediators such as DC and NK cells that ultimately stimulate T-cell function by secreting cytokines and freeing TAA and "danger" signals (e.g., heat shock proteins, HSP; double stranded DNA, dsDNA) from tumor cells. [29]

Table -2 :Types Of Immunoadjuvants

Adjuvant	Category	Activity
Bacillus Calmette-Guerin (BCG)	Bacterial	Nonspecific immunostimulator
DETOX	Bacterial (detoxified endotoxin)	Nonspecific immunostimulator triggering antibody and cell-mediated immunity
Incomplete Freund's adjuvant	Emulsifier and mineral oil	Allows for slow antigen release and extended exposure of antigen to cells
Keyhole limpet hemocyanin	Immunogenic Protein	Elicits CD4 response Augments NK cell activity
IL-12	Cytokine	Activates NK cells and T cells to make many cytokines
GM-CSF	Cytokine/growth factor	Upregulates MHC class II expression Potentiates antigen presentation by dendritic cells Possibly, secretion of GM-CSF by tumor cells increases tumor-specific immunity
Aluminum hydroxide (Alum)	Gel-type	Enhance humoral response

Two major classes of adjuvants commonly found in modern vaccines include:

Vehicles

These are the components which show the increased immune specific response against antigen which presents vaccine antigen to immune system in most selective manner like controlled release and depot delivery system. The vehicle can also serve to deliver immunostimulants. Examples include: mineral salts, emulsions, liposomes, virosomes (nanoparticles made of viral proteins like influenza hemagglutinin and phospholipids), biodegradable polymer microspheres, Quil A, QS 21, and immune stimulating complexes (i.e. ISCOM, ISCOMATRIXTM). [19]

Immunostimulants

Defined as component that directly engage the immune system to increase responses to antigens (e.g. TLR/NLR/RLR ligands, cytokines, saponins, and bacterial exotoxins that stimulate immune responses. While there have been spectacular successes obtained with tumor targeted passive immunotherapy with Rituxan and Herceptin the leading examples, the next challenge is to develop a therapeutic vaccine approach that induces an effective and durable anti-tumor response. [20]

Immunological adjuvants (IA) are agents of very different nature (e.g., microbial extracts, cytokines aluminum hydroxide, and so on) that mixed with an antigen enhance the immune response against that antigen after immunization. Bacterial products (e.g., BCG, Detox) have been used for many years as IA for cancer vaccines. [29]

Combining Vaccines With Conventional Therapies For Cancer

Combination therapy is the emerging option for cancer treatment. In these type two or more treatment are employed in combination with vaccine. The most commonly used option is surgery, chemotherapy and radiation. Hormonal therapy is also used in combination. If cancer vaccines prove viable, there is a good chance they will find use in combination therapy programs. [21]

Early studies have suggested that patients treated with a cancer vaccine before other therapies may have better chances. This is still mostly conjectural, and it will be years before we have enough clinical experience to establish regimen guidelines.

Tumour cells may evade immune responses by altering expression of specific molecules on the target cell. Therapies aimed at modulating these molecules are potentially an important approach to cancer treatment because they may make tumour cells more susceptible to killing by T-cells of moderate avidity. Cytokines, chemotherapy agents and radiation have been examined for this purpose. Non-lethal doses of radiation can be used to up-regulate Fas, intracellular adhesion molecule-1, carcinoem- bryonic antigen, mucin gene-1 and major histocompatibility class I expression on tumour cells, reducing the threshold for killing of T-cells. The response of whole cell vaccine is enhanced by doxorubicin, Cyclophosphamide and Paclitaxel by secreting granulocyte macrophage-colony stimulating factor in HER-2/ neutolerized mice. 5-fluorouracil, etoposide and quercetin dramatically increase the susceptibility of cervical carcinoma cells to killing of T-cells via CD40 ligand-induced apoptosis by disrupting CD40-induced survival signals. [11]

Vaccine plus radiation

Radiation therapy act by direct cytotoxic effect locally at tumor cell. It is frequently employed as a curative and/or palliative approach; it also used to change the tumor structural design, which is responsible for even more delivery system. [5] In 2012 update by National Cancer Institute completed study on vaccine therapy and radiation to liver metastasis in patients with CEA-positive Solid tumors.

Vaccine plus chemotherapy

Chemotherapy is the important in cancer treatment but it will not stand alone, in recent it has been shown that vaccine therapy with chemotherapy will be used to synergistic action by appropriate dosage scheduling. (Table 3)

Combination Chemotherapy is the single most effective treatment for unselected patients with metastatic breast cancer. Various regimens produce Various regimens produce objective remissions in 50% to 80% of patients, with median remission times of 6 to 12 months and survival durations from 12 to 27 month. [22]

Table 3:Potential Mechanisms Of Chemotherapeutic Enhancement Of Immunotherapy

Chemotherapeutic Agents	Mechanism of enhancement
Flurouracil	Change tumor phenotype
Cyclophosphamide	Decrease negative immunoregulatory cells
Doxorubicin	Promotes capase 3-dependent apoptosis

Vaccine plus hormone therapy

There is growing awareness in combining androgen-deprivation therapy (ADT) and vaccine in the management of prostate cancer. It showed that ADT induces profuse T-cell infiltration of benign glands and tumors in the human prostate. [23]

Different Vaccine Delivery Systems For Cancer Therapy

Delivery System in DNA Vaccine

During the last decade, DNA-based vaccination has been promoted as a new approach to major specific humoral and cellular immune responses to protein antigens.

Two basic strategies have been functional for increasing DNA vaccine potency including a) physical delivery to attain higher levels of antigen production and b) formulation with micro particles to target antigen-presenting cells (APCs). [23, 24]

Generally, the techniques of delivering a DNA plasmid are divided into

I) Physical approaches including:

1. Tattooing
2. Gene gun
3. Ultrasound
4. Electroporation
5. Laser

II. Viral and non-viral delivery systems (Non-physical delivery methods) including:

1. Biological gene delivery systems (viral vectors)
2. Non-biological gene delivery systems (non-viral vectors) such as: Cationic lipids/liposomes, Polysaccharides and cationic polymers, Micro-/Nano-particles, Cationic peptides/Cell-penetrating peptides (CPP)

Delivery systems in dendritic cell-based vaccines

DCs offer a direct relationship between innate and adaptive immune response, also arise from bone marrow precursors that are there in immature forms in peripheral tissues, wherever they are prepared to arrest antigens. The delivery of antigen into DCs via the endocytosis pathway, is carried out by Different types of antigen delivery carriers like liposome's, poly-(-glutamic acid) nanoparticles and cholesterol pollutant nanoparticles have been used. Besides this induction of cross presentation of exogenous antigen for DCs on MHC class I molecules is done IgG modified liposome's with entrapped antigen.

The most successful clinical trial for renal carcinoma exploited subcutaneous application. DC vaccination trials for melanoma utilized a combination of subcutaneous and intradermal application with IV boosting, or intranodal route. [24]

Delivery systems in protein/peptide vaccination

Numerous strategies have been reported together with directly conjugating TLR ligand to protein antigens/co encapsulating immunostimulator agent and proteins in liposomes and hydrophobic polymeric particles.

Mucosal delivery systems

The response against infectious disease and cancer achieved by prophylactically and beneficially induced by active mucosal immune system. Unlike challenges are allied with dissimilar use of particle-mediated delivery systems

Conventionally, vaccines are administered by injection (e.g., intramuscular vaccination) and will most probably obtain systemic immune responses but simply unsatisfactory mucosal responses.

The U.S. Food and drug administration (FDA) approved vaccine:

The U.S. Food and Drug Administration (FDA) has approved two vaccines, Gardasil® and Cervarix®, which are used against disease caused by two types of HPV types 16 and 18, these responsible for 70 percent of cervical cancer cases worldwide. Seventeen other types of HPV are accountable for the residual 30 percent of cervical cancer cases. HPV types 16 and/or 18 also cause several vaginal, vulvar, anal, penile, and oropharyngeal cancers. [1, 30]

gardasil

GARDASIL is base on HPV antigens proteins prepared by Merck which are used in to formulate four types of "virus-like particles"; these are HPV types 6, 11, 16, and 18. It is also kwon as quadrivalent vaccine because it made from four type of VLPs combination. Unlike traditional vaccines, which are made up of destabilized whole microbes, VLPs are not infectious. However, the VLPs in Gardasil are still capable to arouse the production of antibodies against HPV types 6, 11, 16, and 18. Seventy-five percent of cervical cancer cases and 95 % GENITAL warts cases can be protected against HPV in younger females (age group of 9 to 26). In boys and young men ages 9 to 26, and also protect against 90% of genital warts cases. [35]

It also helps to protect girls and young women ages 9 to 26 against 70% of vaginal cancer and 50% of vulvar cancer cases. The dosage of GARDASIL is for 3 injections for duration of 6 months.

The most common side effects are Dizziness, Pain, itching, bruising, and redness at the injection site, swelling, Headache, Fever, Nausea, Vomiting and Fainting

Cervarix®

Cervarix, manufactured by GlaxoSmithKline, it is bivalent vaccine, as it is made up of two VLPs (i.e. proteins from HPV types 16 and 18). It is shown that Cervarix have partial protective action against some other HPV type which can cause cancer. However, more studies will be needed to understand the magnitude and impact of this effect. [36]

CERVARIX® is indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18

- Cervical cancer,
- Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ, and
- Cervical intraepithelial neoplasia (CIN) grade 1.

CERVARIX is approved for use in females 9 through 25 years of age.

In April 2010, the FDA approved the first cancer treatment vaccine. Sipuleucel-T (Provenge®) is the vaccine manufactured by Dendreon. Used for treatment of metastatic prostate cancer in men. It stimulates an immune response to prostatic acid phosphatase (PAP); it is antigen that is found on most prostate cancer cells. In clinical trials it is observed that certain type of metastasis prostate cancer the survival increased by 4 months.

Therapeutic Cancer Vaccines Market

The current cancer vaccine market is highly fragmented, and comprises at least 78 clinical development agents. At present, 18% of these pipeline candidates are in Phase III clinical trials or pre-registration, whereas 33% and 49% are in Phase II and Phase I clinical trials, respectively. The pipeline is dominated by antigen specific cancer vaccines. At least 64 companies are involved in clinical R&D, 80% of which are small biotechnology firms. Strategic collaborations with established oncology players will expedite the path to market by providing the marketing and development expertise, as well as financial resources, necessary to negotiate the unique clinical, strategic and regulatory challenges that the commercialization of cancer vaccines presents. [32]

Selected Cancer Immunotherapeutics In Development [37, 38]

Company	Product	Cancer type	Type	Comment/trial stage
GlaxoSmithKline	MAGE-A3	NSCLC	Developed by Ludwig Institute for Cancer Research	Phase 3
Apthera	NeuVax	Prostate, pancreatic, HER2-positive breast	Peptide based	Phase 3 for early-stage HER2-positive breast cancer was to begin late 2007. In Phase 1/2 trials for prostate cancer.
Cell Genesys	GVAX	Prostate, pancreatic, leukemia	Cell-based adenovirus technology	Phase 3 (VITAL-1) trial compares GVAX with Taxotere on survival improvement. VITAL-2, currently enrolling, will compare GVAX plus Taxotere with Taxotere alone.
GlobeImmune	GI-4000	Pancreatic	Protein-based targeted molecular immunogenic technology	Phase 2 in United States and India
Genitope	MyVax	NHL, CLL	Patient specific	Phase 3
Intracel	OncoVAX	Colon	Patient specific	FDA granted SPA for phase 3 study

Merck GKaA Biomira	Stimuvax	NSCLC	Peptide based	Phase 3 enrollments, Feb. 2007. On Sept. 27, Biomira became Oncothyreon.
Northwest Biotherapeutics	DCVax-Brain	Glioblastoma multiform brain tumor	Patient specific	Approved in Switzerland June 2007. Also developing DCVax for prostate cancer.
Pharmexa	GV1001	Pancreatic	Peptide based; uses patented platform technology AutoVac for creation of "pharmaccines" (therapeutic vaccines)	Two phase 3 trials in U.K; U.S. approved in 2009

Present and Future of Cancer Vaccines

In different studies conducted in animals it has been observed that vaccines have caused cancers to retreat. The situation is more complex in Humans. Cancers have developed ways of escaping the immune system. Presently the studies shown discovered that how cancer cells will avoid recognized by immune system.

Therapeutic cancer vaccines have shown promise in early-stage clinical trials against several types of cancer:

In one early-stage study, patient who was given an autologous vaccine shows boost the immune response. In some patients with advanced non-small cell lung cancer had a complete remission of disease. The cells release a substance called granulocyte-macrophage colony-stimulating factor (GM-CSF) in great amounts. GM-CSF boosts the immune system's ability to protect against cancer.

Some researchers are looking at a vaccine called Oncophage as a possible treatment for kidney and skin cancers. This vaccine is specially made for each patient, using a tumor's own "blueprints." Scientists identify what makes the cancer cells in the tumor different from normal, healthy cells. Then, they create a vaccine that trains the immune system to recognize and destroy the cancer cells without harming normal cells.

For the effectiveness of vaccine in treatment of cancer have lot to understand. It is possible that vaccines will prove more effective when combined with other therapies and that multiple vaccinations may be necessary for a benefit to be seen.

Much work also remains to be done to develop vaccines that can reliably prevent cancers associated with infectious agents. Cervical cancer, for example, is almost always caused by infection with HPV. The FDA has approved a vaccine that prevents infections with two types of HPV that cause nearly 70 percent of all cervical cancers. Researchers must develop new vaccines that are able to prevent infections by all HPV types that can cause this disease. The current ongoing clinical trials carried out for hopefully situation cancer treatment, and FDA will only consider the vaccine for treatment which provided the more evidences of safety.

CONCLUSION

There are many aspects of commercializing cancer vaccines that will require developers, regulatotrs and clinicians to collaborate on an unprecedented level to expedite the delivery of these new therapies to patients. One of the single biggest challenges will be to bring together the keepers of disparate intellectual property for example, vaccine-delivery technologies, immune adjuvants and formulation techniques and combining these pools of expertise to produce effective cancer vaccines with broad clinical application. On the basis of forecast peak sales and the assumption that the most promising Phase III pipeline candidates are granted marketing approval, Datamonitor estimates that the potential worth of the therapeutic cancer vaccine market will be US$633 million by 2014.

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