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Essence of Immunotherapy In Developing Cancer Vaccines.

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ABSTRACT

Cancer is a tumour or malignant growth caused by abnormal and uncontrolled cell proliferation. Morbidity and mortality associated with cancer is increasing in developing as well as developed countries. It accounts for about 7.4 million deaths per annum. Cancer vaccines are biological response modifiers work by stimulating or restoring the immune system's ability to fight against cancer. It is an emerging therapy but still clinical trials are underway to test vaccines as potential treatments for a wide variety of cancer types. Genetic and epigenetic characteristic changes of oncogenesis make cancer cells antigenically distinct from normal human cells. Cancer cells express tumor-specific antigens and tumor-associated antigens. Tumor-specific antigens are ideal targets for antitumor therapy. Even though cancer vaccines appear as promising therapy, developing cancer vaccine is problematic due to the specificity of tumour antigens and weakness of tumour associated antigens in eliciting an effective immune response.

Keywords: Cancer vaccines, immunotherapy, prevention vaccine, treatment vaccine

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INTRODUCTION

Immunology is a branch of medical science that deals with body's immune system. Immune system refer to system (includes thymus, bone marrow and lymphoid tissues) that protects the body from various foreign substances and pathogenic substances by producing immunologic response [1]. Cancer is a tumour or malignant growth caused by abnormal and uncontrolled cell proliferation which may spread to other parts of the body through lymphatic circulation or blood stream. Now-a-days morbidity and mortality associated with cancer is increasing in developing as well as developed countries. About 80% of cancers are predominantly due to fourteen types of cancer which includes prostate cancer, hepatic cancer, breast cancer, lung cancer, gastric carcinoma, colon cancer, bladder carcinoma, skin cancer, ovarian cancer, renal cell carcinoma, brain cancer, leukemia, pancreatic cancer and testes cancer [2]. The survey conducted by International agency for research on cancer revealed that the burden of cancer will be doubled in next 20 years. Cancer accounts for about 7.4 million deaths per annum and a higher rate of mortality is observed due to lung cancer which accounts for about 1.3 million deaths /annum, followed by about 803,000 deaths /annum due to gastric carcinoma, subsequently colon cancer accounts for about 639,000 deaths /annum, mortality due to hepatic carcinoma accounts for about 610,000 deaths /annum. Breast cancer has a higher prevalence in India whereas death due to breast cancer is minor, about 519,000 deaths per annum [3]. Epidemiologic studies in 2000 estimates about 10 million new cases would be reported per annum but WHO estimates 15 million cases would be reported per annum by 2020 [4]. According to conventional allopathic medicine more than 150 types of cancer are present which are classified based on the site of origin i.e., carcinoma, melanoma, sarcoma, leukaemia, lymphoma and glioma [5, 6]. Currently many treatments are available for cancer. Commonly used treatments are surgery, chemotherapy, radiation therapy; in specific cases - hormone therapy, immunotherapy and stem cell treatment. Most of the people will be aware of all the therapies which are available for cancer but only few people know about immunotherapy. Immunotherapy aims to enhance the immune system to cure diseases. These types of therapies help to activate immune cells (T or B cells) to fight against cancer cells. These products usually contain anti bodies or immune factors that aid in promoting passive immune responses exploiting the fact that cancer cells possess antigens that are subtly different from normal human cells [7, 8].

Cancer Vaccines

Cancer vaccines are medicines that belong to a class of substances known as biological response modifiers. Biological response modifiers work by stimulating or restoring the immune system's ability to fight against infections and disease. Primarily, Cancer vaccines are classified into two types based on the effect. They are prevention (prophylactic) vaccines and treatment (therapeutic) vaccines. Cancer prevention vaccines are usually administered to healthy persons as prophylaxis against certain cancer. Examples of cancer prevention vaccines approved by the Food and Drug Administration (FDA) are: i) Gardasil (prevents cervical, vaginal and vulvar cancers in girls and women; Anal cancer in women and men; Genital warts in men and boys) ii) Cervarix (protects against human papilloma virus infection for the prevention of cervical cancer in girls and women) [9] iii) Hepatitis B vaccine (prevents hepatitis B virus (HBV) infection. Long-lasting infection with HBV can cause hepatic cancer) [10]. Cancer treatment vaccines work by promoting body's natural defence mechanism to fight against cancer. These are usually prescribed in patients diagnosed with cancer. They prevent cancer recurrence, destroy cancer cells remaining in the body after treatment and stops metastasis of tumour cells [11]. Examples of cancer treatment vaccines approved by FDA are: i) Sipuleucel-T (to treat metastatic prostate cancer); ii) Talimogene laherparepvec (to treat metastatic melanoma). The aim of cancer vaccines is to stimulate the immune system to be able to recognize cancer cells as abnormal and destroy them. This review article provides emphasized information about cancer vaccines and its types along with examples which are FDA approved and also under clinical trials.

PARADIGM OF CANCER VACCINES

There are six different types of vaccines being developed which includes antigen vaccines, tumour cell vaccines, anti-idiotype antibody-based vaccines, dendritic cell vaccines, DNA vaccines and viral-vector based vaccines. Here, we will discuss about each type of cancer vaccine along with examples under clinical trials are shown in Table 1-6 [43-49]

Antigen vaccines

It stimulates immune system by producing tumour specific antigens which are usually proteins or peptides. These are also called as protein or peptide vaccines. Administration of this vaccine into the cancerous tissue induces production of cytotoxic lymphocytes/ natural killer cells which act as antibodies against cancerous tissue that carries antigen [12]. It should possess the ability to differentiate specific tumour cells and normal cells such that the antibodies generated could specifically target tumour cells not normal cells. Most of the cancer antigens used is derived from mutated or altered self-proteins with certain level of immune tolerance. A great challenge is to overcome auto-tumour immunity without autoimmunity and designing an appropriate dosage form. Immunotherapy can be either active or passive immunotherapy. Active immunotherapy is administration of vaccines aimed to elicit immunologic response against specific antigens whereas passive immunotherapy is administration of antibodies or cells isolated in vivo [13, 14]. Scientists developed strategies to change the antigens such that they can be easily recognised by immune system and often tried to combine these antigens in order to provide strong immunologic response [15].

TABLE 1: EXAMPLES OF ANTIGEN VACCINES

PRODUCT NAME	DESCRIPTION	INDICATION	TRIAL PHASE
NY-ESOI	Immunogenic peptide derived from the cancer-testis antigen (NY-ESO-1), an antigen found in normal testis	Hormone-resistant prostate cancer	Phase III
NEUVAX	Immunogenic peptide derived from the Her-2/neu protein and GM-CSF	Early-stage breast cancer (Her-2 +ve)	Phase II
HER2/NEUCANCER	Peptide vaccine comprising of Ii-Key modified Her-2/neu protein fragment	Nodal-negative breast cancer	Phase II
CDX-110	A 14-amino-acid segment of a mutated EGFR	Glioblastoma Multiforme	Phase II
IMA901IMA910	Peptide vaccine consisting multiple fully synthetic tumour-associated peptides	Renal carcinoma, colon cancer	
GV1001	Recombinant protein vaccine which targets human telomerase reverse transcriptase and GM-CSF	Pancreatic lung cancer	Phase III
STIMUVAX	Liposomal vaccine comprising a synthetic 25-Amino-acid-peptide sequence from MUC-1	Non-Small Cell Lung Cancer	Phase III

Tumour cell vaccines

These are actual cells that are obtained from body during surgery. Whole tumour cell vaccines are rich in tumour associated antigens (TAA) so that they can stimulate immune system (CTLs and CD4-T helper cell activation). Sometimes physicians give vaccine along with adjuvants to enhance immunogenicity. Adjuvants are the compounds that enhance the immune responses elicited by the tumour cell vaccines with minimal responses and toxic effects. Alum is the first licensed adjuvant for use in humans [16]. The process of designing adjuvants for cancer vaccines evolved with understanding synergism of conserved pathogen associated molecular patterns (PAMPs) with specific pattern recognition receptors (PRRs). Tumour cell vaccines are of two types: autologous vaccines and allogenic vaccines. As the name suggests autologous vaccine are obtained from cancerous tissue of same individual which are then killed and re-injected into the body whereas allogenic vaccines are obtained from cancerous tissue of an individual other than the patient. The basis of innate immunity is due to downstream signalling resulting in activation of NF-kB and IRF-3 as well as expression of proinflammatory cytokines which are continued to be used individually as recombinant proteins, fusion partners of specific TAAs [17]. Addition of toll like receptors (TLR) agonists leads to development of adjuvants to cancer therapy. TLR-targeted adjuvants are formulated as novel drug delivery systems (micro particles, nanoparticles, liposomes) with selected antigens. Preclinical studies revealed that a triad of co-stimulatory

molecules (TRICOM) elevate T-cell responses to TAA greater than levels elicited by one or two co-stimulatory molecules in combination [18-23].

TABLE 2: EXAMPLES OF TUMOUR CELL VACCINES

PRODUCT NAME	DESCRIPTION	INDICATION	TRIAL PHASE
ONCOVAX	Autologous cancer vaccine consisting of patient's own tumor cells to launch a potent and customized immune response against residual cancer cells	Colon cancer	Phase III
G VAX	Granulocyte-macrophage colony-stimulating factor (GM-CSF) gene-transfected tumor cell vaccine.	Melanoma/ovarian carcinoma	Phase II
M-VAX	Autologous cell vaccine obtained from patient tumor cells treated with the hapten dinitrophenyl	Metastatic melanoma	Phase III
M3TK	Patient's own T-lymphocytes, genetically engineered ex vivo to express the tumour antigen MAGE-3	Malignant melanoma	Phase-I/II
HSPPC	gp96 heat shock protein-peptide complex obtaining from person's tumor cells	Glioblastoma multiforme	Phase III
BiovaxID	Autologous vaccine containing tumor-specific idiotype proteins from patient's lymphoma cells and conjugated to keyhole limpet hemocyanin (KLH)	Non-Hodgkin's Lymphoma	Phase III
IDM-2101	10 synthetic peptides from these TAAs, 9 of which represent CTL epitopes. The tenth is a pan-DR epitope designed to augment the CTL response	Non-small cell lung cancer (NSCLC)	Phase III
Lucanix	Mixture of 4 allogeneic NSCLC cell lines genetically modified to secrete an antisense oligonucleotide to TGF-β2	Lung cancer	Phase III

Anti-Idiotype antibody-based Vaccines

Immunoglobulins are class of proteins with specific peptide sequence which acts as antibodies in immune system. Idiotype refers to a specific peptide sequence of an antibody. On injection, an anti-idiotype antibody appears to be a foreign substance and provokes immune system to attack anti-idiotype with its own antigens. These agents can be used as cancer vaccines as they seems to be an antigen over cancer cells, thereby stimulates production of immune responses against specific cancer [24]. Chemotherapy followed by anti-idiotype seems to be effective therapy. Researchers consider anti-idiotype vaccines to be effective against lymphoma as lymphoma cells possess unique receptors that are not present on normal lymphocytes [25].

TABLE 3: EXAMPLES OF ANTI-IDIOTYPE ANTIBODY-BASED VACCINES

PRODUCT NAME	DESCRIPTION	INDICATION	TRIAL PHASE
11D10 (TriAb)	Monoclonal antibody (MoAB) directed against an idiotype that mimics a human milk fat globule (HMFG) membrane epitope	Breast cancer Colorectal cancer Lung cancer	Phase-II
MK2-23	Mirror image of the antigenic determinant defined by antihuman high molecular weight-melanoma associated antigen (HMW-MAA) mAb 763.74.	Melanoma	Phase III
BR3E4	Monoclonal Ab2 produced against Abl CO17-1A [BR3E4-IgG and BR3E4-F(ab')2-KLH] to modulate	Colorectal cancer	Phase II/III

	humoral and cellular immune responses		
3H1 (CeaVac)	Monoclonal antibody which mimic a specific epitope of the tumor-associated protein carcinoembryonic antigen (CEA).	Colorectal cancer	Phase II
105AD7	Humanized monoclonal antibody that mimics a tumor-associated antigen 791Tgp72 (also known as CD55)	Colorectal cancer	Phase II

Dendritic Cell Vaccines

Dendritic cells (DC) are specialised antigen presenting cells that aid immune system to identify cancerous tissues and stimulate T cells. Dendritic cells are accommodated to appropriate proteins which digest them proteolytically, presenting cancer cells to immune system cells [26]. Dendritic cell vaccines are usually autologous and are made individually from every patient. These vaccines are developed by removing some cells and treating them in lab to multiply and develop into dendritic cells which are then exposed to cancer cells. Other methods to develop dendritic vaccines are through change in genes in order to make their own antigens or to fuse dendritic cells with cancerous cells. Dendritic cells with cancer antigens on their surface aids immune system to recognise and destruct cancer cells that possess similar antigens on their surface. Each subset of DC possesses a unique potential to activate T-Helper (TH1 and TH2) cells. The ability of DC cells to activate T cells can be enhanced through isolation of a particular subset and undergoing maturation process in order to induce superior immune response [27-29]. Studies revealed that concomitant administration of TLR agonists with oligodeoxynucleotides, promotes DC vaccines to break immune tolerance to tumour antigens [30]. Cellular immunotherapy with dendritic cell vaccines provides long term anticancer responses with immune cells contributing to effective elimination of malignant cells [31].

TABLE 4: EXAMPLES OF DENDRITIC CELL VACCINES

PRODUCT NAME	DESCRIPTION	INDICATION	TRIAL PHASE
GRNVAC1	Autologous dendritic cells transfected with mRNA for human telomerase and a portion of lysosome associated membrane protein	Remission stage of Acute Myeloid Luekemia (AML)	Phase III
UVIDEM	Autologous dendritic cell vaccine loaded with antigens derived from resected tumor	Melanoma	Phase II
INGN225	Dendritic cells treated with human p53 gene carrying adenovector	1.Advanced metastatic small cell lung cancer 2.Breast cancer	Phase II
DC-VAX PROSTATE	Dendritic cells that loaded with recombinant prostate specific membrane antigen (PSMA)	Hormone-dependent, non-metastatic prostate cancer	Phase III
DC-VAX BRAIN	Dendritic cells loaded with extract of tumor	Glioblastoma multiforme	Phase III
CVAC	Priming of dendritic cells with a mucin-1 and a mannanfusion protein adjuvant	Late-stage ovarian Carcinoma	Phase II

DNA vaccines

DNA vaccines are genetically engineered bacterial plasmids in order to express encoded protein followed by administration and simultaneous transferability. These vaccines contain transcriptional terminator that terminates the process of transcription in mammalian tissues and thereby facilitate production of plasmids in transformed bacterial cells. Firstly, upon administration encoded protein enters into processing and presenting pathways of immune system and induces adaptive and innate responses similar to natural

infection. Secondly, stimulation of non-specific innate immunity against tumour growth is provided by bacterial DNA [32-34]. DNA vaccines are more advantageous than other vaccines due to ease of production and does not require special handling and storage conditions which elicit immune responses against encoded proteins whereas other vaccines depend on tumour antigen expression which elicit both CD8+ and CD4+ T cell responses. DNA based cells are safe for use in humans [35, 36]. Major disadvantage is that using an oncogenic gene is potential enough to integrate into genome of a cell promoting malignancy [37].

TABLE 5: EXAMPLES OF DNA VACCINES

PRODUCT NAME	DESCRIPTION	INDICATION	TRIAL PHASE
INO-5150	Inovio's DNA-based IL-12 immune activator. The study is evaluating changes in PSA levels, an important biomarker in prostate cancer.	Prostate cancer immunotherapy	phase I
ZYC101	Plasmid DNA encapsulated in biodegradable polymer microparticles. That encodes for multiple HLA-A2-restricted epitopes derived from the HPV-16 E7 protein	Cervical and anal dysplasia	Phase III
VGX-3100	HPV-specific immunotherapy consisting plasmids targeting the E6 and E7 proteins of HPV types 16 and 18	cervical cancer	Phase III
FLT3LG	Murine T-cell line, cloned a novel hematopoietic growth factor that is a ligand for FLT3 (FMS-related tyrosine kinase-3)	AML	Phase III
CureVac	Derived customized mRNA molecules used to encode different tumour-associated antigens with enhanced translational potency and self-adjuvanting activity	prostate cancer and NSCLC	Phase II

Viral-vector based vaccines

These vaccines are of two categories i.e. vector based antigen vaccines and vector based DNA vaccines. These vaccines utilise recombinant viruses as vectors which possess innate ability to express proteins isolated from foreign pathogens and induce production of immune responses against these antigens. These gene based vectors are capable of stimulating potent humoral and cellular immune responses and are thus considered effective strategy for delivery of antigen coding genes facilitating enhancement of antigen presentation [38]. These vectors are usually self-adjuvant that possesses ability to express multiple TAAs with a range of immune co-factors. The major limitation of these vectors is that host-based immune responses can neutralise these vectors on repeated use. The advantages of these vectors are that they can mimic a natural infection by providing optimal activation of antigen presenting cells (APC), less expensive and it can deliver more than one cancer antigen [39]. The first developed vector based vaccine is Vaccinia, a pox virus developed 20 years ago. Other vaccines developed are based on pox virus include modified Vaccinia virus Ankara, and avian pox viruses- fowlpox and canarypox [40].An additional advantage is feasibility of administering viral vector based vaccines in combination with other type of vaccines. Preclinical trials in mice immunised with combination therapy of Ad5-PSA and CpG shown enhanced protection against cancerous tissue compared to mice immunised with vaccine alone [41]. A prophylactic quadruple HPV 6/11/16/18 vaccine is effective in reducing risk of HPV 6,11,16,18 associated anogenital disease. Immunization with vector based vaccines is effective in reducing overall burden of clinical HPV disease [42].

TABLE 6: EXAMPLES OF VIRAL-VECTOR BASED VACCINES

PRODUCT NAME	DESCRIPTION	INDICATION	TRIAL PHASE
PSA-TRICOM	Novel vector-based vaccine designed to generate a robust immune response against prostate-specific antigen (PSA)-expressing tumor cells	Metastatic hormone refractory prostate cancer	Phase III

PANVAC-VF	Recombinant vaccinia virus and booster doses of recombinant fowlpox virus expressing carcinoembryonic antigen, mucin-1 and a triad of costimulatory molecules (TRICOM)	Pancreatic cancer	Phase III
MVA-E2	Recombinant vaccinia vector encoding the E2 viral protein	Cervical intraepithelial neoplasia	Phase III
TG4001	Immunotherapy targeting the MUC1 protein	Advanced NSCLC	Phase II
rAd-p53	Recombinant adenoviral vector encoding human tumor-suppressor protein p53 gene	Advanced oral and maxillofacial malignant tumors	Phase IV
ADXS11-001	Live-attenuated strain of the bacterium Listeria monocytogenes (Lm) encoding human papillomavirus (HPV) type 16 E7 fused to a non-hemolytic listeriolysin O protein	Recurrent cervical cancer	Phase II

CONCLUSION

Cancer is the leading cause of death after heart disease and also a major health problem worldwide requiring new treatment modalities and new strategies to combat the disease. Even though cancer vaccines appear as promising therapy, developing cancer vaccine is problematic due to the specificity of tumour antigens and weakness of tumour associated antigens in eliciting an effective immune response. Targeting of tumor specific antigen is difficult, since it varies from individual to individual necessitating the need for personalized treatment. Therefore, computational models can play an effective role in prediction and optimization of therapeutic effects of cancer vaccine which is necessary for personalized treatment.

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