

Recent Advances in Cancer Vaccines – An Update

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Abstract: Cancer related deaths have shown a progressive increase over the past decade and the newer cases of cancers are estimated to rise in 2030. The current treatment modalities available for cancer are highly toxic, impair quality of life and develop resistance with course of time. Thus, there is a growing necessity for the prevention and cure of cancer related morbidity and mortality. One of the promising approaches for cancer prevention could be immunization with specific vaccines. The latest advances in immunology have led to the development of effective cancer vaccines to enhance immunity against tumour cells. Moreover, the occurrence of cancer with infectious agents like Hepatitis B virus (HBV) and Human Papilloma virus (HPV) as well as their prevention with specific cancer vaccines has further confirmed the role of immunotherapy in cancer. Though prophylactic vaccines are found to be more successful in cancer prevention, in the present scenario most of the vaccines under development are therapeutic cancer vaccines.

Cancer vaccines stimulate the immune system and attack specific cancer cells without harming the normal cells. The major cancer vaccines under development to target tumour cells includes antigen vaccines, whole cell tumour vaccines, dendritic cell vaccine, viral vectors, DNA vaccines and idiotypic vaccines. Apart from this, measures to produce patient-specific cancer vaccines from patients own tumour cells and a "universal" vaccine to provide immunity against cancer cells of any origin are being investigated. Hence this review gives an overview of various strategies involved in the development of cancer vaccines and the currently approved vaccines available for the prevention of cancer.

Keywords: Immunotherapy, peptide vaccine, DNA vaccine, gardasil, cervarix, Sipleucel.

INTRODUCTION

Cancer has been one of the leading causes of disease related deaths in developed as well as developing countries. Over the past decade, there has been an alarmingly progressive increase in the occurrence of malignancy owing to a rising elderly population [1]. New cases of cancers are estimated to rise from 11.3 million in 2007 to 15.5 million in 2030. Similarly, the global cancer death has been projected to increase from 7.9 million in 2007 to 11.5 million towards 2030 [2]. This has set a lot of pressure on the healthcare system, to approach newer and economical measures for prevention and cure of cancer related mortality. The treatment modalities available for cancer in the present scenario include surgery, chemotherapy and radiotherapy. However chemotherapy and radiotherapy are either highly toxic, impair quality of life or develop resistance with course of time [3, 4]. As 40% of all cancer deaths are avoidable, one of the most promising approaches for cancer prevention and treatment could be immunization with specific vaccines [2].

The concept of immunotherapy for cancer was first shown by William B. Coley, the "Father of Immunotherapy," with the disappearance of tumour, following streptococcal infection in a cancer patient [5].

This was followed by several advances in immunology that ultimately led to the development of effective cancer vaccines to enhance immunity against tumour cells [6-8]. In addition, the occurrence of cancer with infectious agents like Hepatitis B virus (HBV) and Human Papilloma virus (HPV) as well as their prevention with specific cancer vaccines has further confirmed the role of immunotherapy in cancer. Though prophylactic vaccines are found to be more successful in cancer prevention (Tables 1 and 2), currently most of the vaccines under development are therapeutic cancer vaccines.

The therapeutic cancer vaccines stimulate the immune system to recognize and attack specific cancer cells without harming the normal cells [9-13]. These vaccines reduce further growth of existing tumour cells and eliminate the malignant cells resulting in reduced recurrence and increased survival rate [14, 15]. The therapeutic vaccines under development includes peptide and protein vaccines, whole cell tumour vaccines, dendritic cell vaccine, RNA vaccines, DNA vaccines and idiotypic vaccines [16]. Apart from this, measures to produce patient-specific cancer vaccines from the patient's own tumour cells and a "universal" vaccine to provide immunity against cancer cells of any origin are also being tried [17-19]. Hence this review deals in detail, the various strategies involved in the progress of cancer vaccines and the steps taken to improve their specificity against cancer prevention and treatment.

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Table 1: Infectious organisms associated with malignancy

Infectious agent	Associated cancer
Hepatitis B virus (HBV), Hepatitis C virus (HCV)	Hepatocellular carcinoma
Human papilloma virus (HPV)	Cervical cancer, vaginal cancer, vulval cancer, oropharyngeal cancer, anal cancer, penile cancer
Epstein Barr virus (EBV)	Burkitt lymphoma, non Hodgkin lymphoma, Hodgkin lymphoma, nasopharyngeal cancer
Human T-cell lymphotropic virus 1 (HTLV1)	Acute T-cell leukemia
<i>Helicobacter pylori</i>	Stomach cancer
<i>Schistosoma hematobium</i>	Bladder cancer
Liver flukes (<i>Opisthorchis viverrini</i>)	Cholangiocarcinoma

Table 2: Currently approved cancer vaccines and their indications [10]

Cancer vaccines	Indications	Current status
<u>Gardasil</u> Human Papillomavirus Quadrivalent Recombinant Vaccine, (Types 6, 11, 16, 18)	a. Cervical cancer b. Genital warts (condyloma acuminata) c. Cervical adenocarcinoma <i>in situ</i> (AIS) d. Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3 e. Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3 f. Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3 g. Cervical intraepithelial neoplasia (CIN) grade 1	US FDA approved - Vaccination in females 9 to 26 years of age for prevention of cervical cancer caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 Vaccination in boys and men 9 to 26 years of age for the prevention of genital warts caused by HPV types 6 and 11 which do not cause malignancy
<u>Cervarix</u> Human Papillomavirus Bivalent Recombinant Vaccine (Types 16 and 18)	a. Cervical cancer b. Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma <i>in situ</i> , and cervical intraepithelial neoplasia (CIN) grade 1, caused by oncogenic human papillomavirus (HPV) types 16 and 18,	US FDA approved for prevention of cervical cancer, in females 10 to 25 years of age
<u>Sipuleucel-T (Provenge)</u>	Prostate cancer	US FDA approved
<u>Oncoophage</u>	Brain cancer, metastatic melanoma, renal cancer	Orphan drug status in Europe

IMMUNOTHERAPY IN CANCER

Cancer vaccine development focuses on the understanding of specific tumour antigens against which both humoral and cellular immune responses are elicited [20, 21]. Tumour specific antigens (TSA) expressed on the tumour cells are unique to cancer cells and they can be either products of mutated normal cellular genes or viral antigens. The characteristic features of various tumour specific antigens are shown in Table 3 [22, 23]. On the contrary, tumour associated antigens (TAA) are expressed in both normal and cancer cells but in diverse ways [24]. However, many tumour antigens are not expressed on the surface of tumour cells and as a result, they are remote to the antibodies [25, 26]. This

can be overcome by designing various strategies to stimulate the immune system against TAA.

One of the approaches used for the generation of more immunogenic tumour antigen is to identify unique tumour cell antigens that are present very rarely on normal cells and alter their amino acid structure. Another method could be, attaching an adjuvant like incomplete Freund's adjuvant (IFA) also known as Montanide ISA51 with tumour antigens for enhancing the immune system against both the antigen/adjuvant complex and the patient's tumour [27, 28]. The adjuvant has been found to be more effective in inducing antibody (Th2) response than cellular (Th1) immune responses [29-31].

Table 3: Characteristics of tumour specific antigens (TSA) [22-23]

Type of tumour antigens	Characteristics	Examples
Unique tumour antigens	Specific to tumour	Mutant Epidermal Growth Factor Receptor (EGFR) – found in glioblastoma Prostate Specific Antigens (PSA) - produced in large amounts by prostate cancer cells than by normal prostate cells
Shared tumour antigens	Expressed in many tumours but not in normal adult tissue	Carcinoembryonic Antigen (CEA) - found in fetal tissues, stomach cancer, colon cancer, breast cancer Mucin-1 (MUC1) - found in mucus producing epithelial cells, breast, prostate, colon, pancreatic cancer, multiple myeloma HER2/neu protein - over expressed in breast, ovary cancer Gangliosides (GM3 & GD2) - found in the outer membrane of several types of cancer cells, including melanoma, neuroblastoma, soft tissue sarcoma, small cell lung cancer
Over expressed tumour antigens	Markedly over expressed in different types of cancers including hematologic tumours	proteinase-3 (PR-3) – AML,CML Wilm's tumour gene-encoded transcription factor-1 (WT-1) - AML,CML
Tumour suppressor gene and oncogene as tumour antigens	Many tumours	p53, Ras
Viral-associated antigens	Adult T-cell leukemia Hodgkin's lymphoma	HTLV-1 EBV

Dendritic cells (DC) generated under the influence of cytokines act as antigen-presenting cells (APC) and represent one of the most powerful naturally occurring immunological adjuvants for anticancer vaccines [32, 33]. These cells induce tumour-specific immunity by directly activating natural killer cells (NK) and increase the synthesis of interferons following their encounter with viral antigens [34-36]. Moreover DCs secrete cytokines like IL-12 and IL-15 that contribute to cytotoxic T lymphocytes (CTLs) activation and memory as shown in Figure 1 [37].

DCs treated with drugs like vincristine, vinblastine, paclitaxel, 5-aza-2-deoxycytidine and methotrexate showed an increased expression of co stimulators CD83 and CD40 which play an important role in activating CTL precursor. Moreover, 5-aza-2-deoxycytidine, methotrexate, and mitomycin C have been shown to augment the ability of DCs to boost T lymphocyte proliferation [2, 38, 39]. In murine tumour models, DC loaded with tumour antigens have demonstrated protective immunity with regression of established tumours [38]. This has been further confirmed by clinical findings associated with tumour regression following DC-based active specific immunotherapy in some cases [36].

One of the newer approaches in designing targeted cancer vaccines is using genetic materials to encode

the tumour specific antigens. These vaccines are delivered into the host antigen presenting cells (APC) like DCs by means of viral vectors or naked DNA [40, 41].

Among the gene therapy vaccines, DNA vaccines containing the gene for a specific cancer antigen is manipulated in such a way to be taken up and processed by antigen-presenting cells (APCs). Thus following administration of APC into a patient, the immune system will start responding towards both APC and tumour cells containing the same antigen. DNA vaccines express the encoded protein in its natural form into the host cell without any further modification. Moreover, they can cause prolonged expression of the antigen, and generate significant immunological memory in the host. DNA vaccines introduce tumour antigen genes into the DCs for presentation to CTLs in the draining lymph nodes, without the need for a viral vector. Hence following DNA vaccination, the CD8+ T-cell priming has shown to confer protection against both infections and tumours [42].

Peptide vaccines function through APCs that sensitize and activate a CTL response as shown in Figure 2. Vaccination with tumour-specific peptides introduces a distinct tumour antigen *in vivo* resulting in its internalization by APC and effective presentation to reactive T cell clones. The resultant expansion of

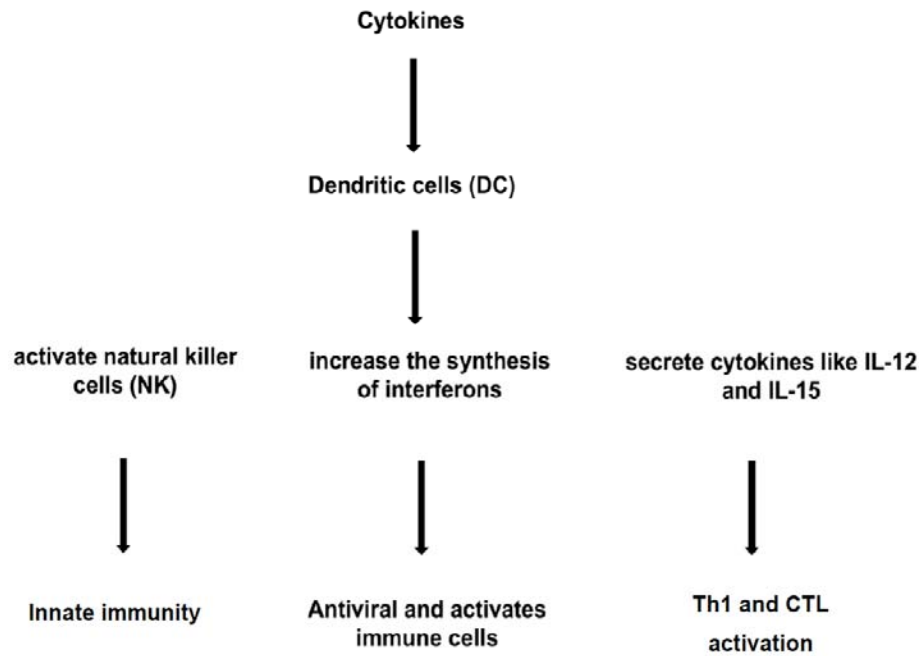


Figure 1: Effect of dendritic cells (DC) on cell mediated immunity.

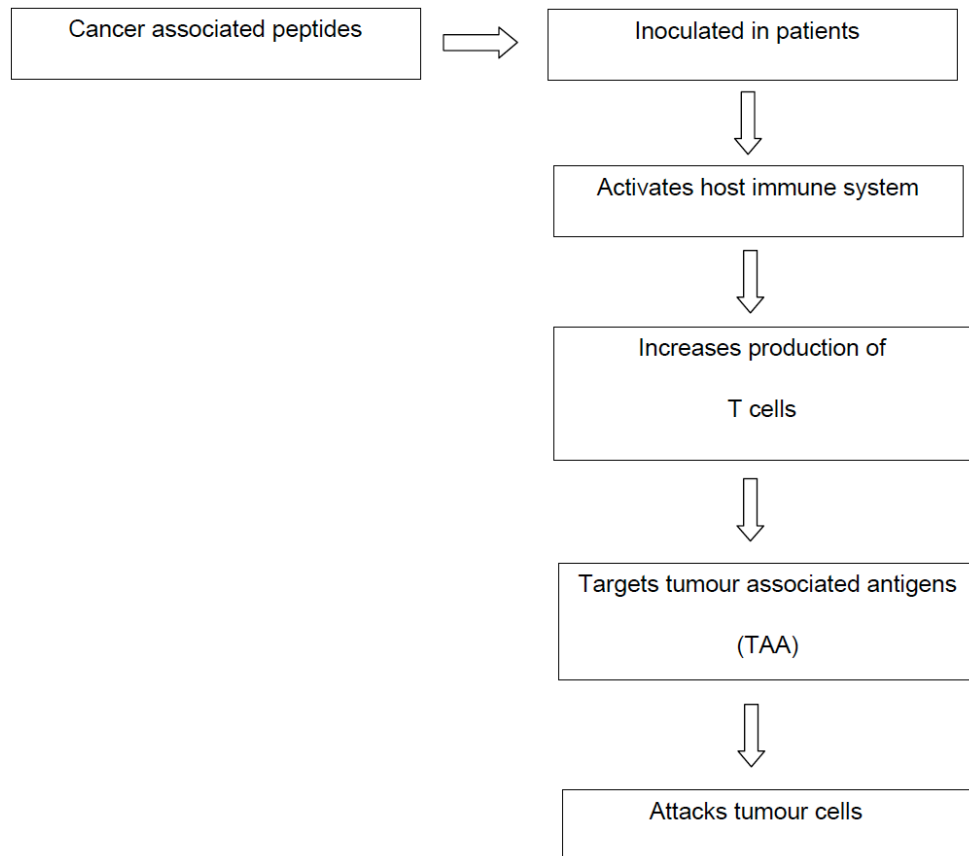


Figure 2: Schematic diagram showing strategy used to induce immunity using peptide based vaccines.

cytotoxic T cells helps in targeting the tumour cells bearing the same epitope resulting in optimization of T-cell activation with more potent response [43]. Production of peptide – based vaccines is relatively

simple and cost effective and their efficacy can be increased with addition of adjuvants like cytokines [44, 45]. Thus a recent strategy for the development of peptide vaccines is to combine cytokines like GM-CSF

and co-stimulatory molecules like CD40L that induce DC recruitment as well as maturation respectively [46]. However the major drawbacks of peptide vaccines are low bioavailability and poor metabolic stability [47, 48].

PROPHYLACTIC CANCER VACCINES

One of the key intentions of cancer vaccine development is to afford a cost-effective vaccine that can prevent and treat premalignant diseases. Since infectious agents like *Hepatitis B virus (HBV)*, *Hepatitis C virus (HCV)*, *Human papilloma virus (HPV)* and *Helicobacter pylori* represent the major cause of infection induced malignancies, presently prophylactic vaccines are being investigated against the cancer due to these infections. Some of the vaccines against these infections are already available in the market and have shown success rate in preventing cancer with improved survival [9,10].

Hepatitis B Virus (HBV) Cancer Vaccines

HBV infection accounts for nearly one million deaths worldwide per year. Of this, one-third of deaths are attributed to infection induced hepatocellular carcinoma (HCC). The HBV vaccine using hepatitis B surface antigen as a subunit, is the first and the most successful prophylactic vaccine to be used against a cancer inducing infectious agent. HBV vaccine has been found to reduce HBV titre in blood, thus reducing the risk of HCC and chronic liver disease in HBV carriers. Moreover this vaccine has shown decreased occurrence of HCC in countries like Taiwan and China [49-51].

HPV Vaccines

Human papilloma virus (HPV) is known to cause benign genital warts and pre invasive neoplasm that have the potential to progress to cervical cancers [52, 57]. Among the HPV virus types, HPV-16 and HPV-18 contains E6 and E7 oncogenes and are responsible for 70% of the cervical cancer [50]. Cervical cancer can be prevented with well organized screening of the risk population and intervening at the right time with prophylactic vaccines [53]. Presently two prophylactic vaccines namely Gardasil and Cervarix are found to be highly efficacious and approved in many countries for the prevention of cervical cancer due to *HPV 16 and 18* [53, 54].

Gardasil, a quadrivalent recombinant vaccine was approved by USFDA in 2006 for prevention of cervical cancer in girls and women of age 9-26 yrs caused by

HPV 6, 11, 16 and 18 [55-57]. Gardasil also protects against HPV 6 and 11, that do not cause malignancy [58]. Recently in October 2009, USFDA extended the approval for Gardasil vaccination to boys and men of 9 to 26 years of age for the prevention of genital warts caused by HPV types 6 and 11 [59]. Similarly a newer vaccine Cervarix approved by USFDA in October 2009 has been found to be effective against the five most common types of cervical cancer inducing HPV -16, 18, 31, 33 and 45 [10]. The duration of efficacy against cervical cancer has been estimated to be around 6.4 years with cervarix compared to that of 5 years with Gardasil [59-61].

PROSTATE CANCER

The presence of tumour-associated antigens like prostate-specific antigen (PSA), prostatic acid phosphatase (PAP) and prostate-specific membrane antigen (PSMA) has made immunotherapy an attractive option for prostate cancer [62]. Prostate specific antigens (PSA) are usually present in low levels in normal men, and increases with progression of prostate cancer. The higher the PSA level, it is more likely that prostate cancer is present, though there may be other possible reasons.

At present, one of the prostate cancer vaccines, namely Sipuleucel-T composed of autologous antigen-presenting cells and a fusion protein made of prostatic acid phosphatase with granulocyte macrophage colony-stimulating factor has been approved by USFDA for therapeutic use. This vaccine has shown increased T-cell response and decrease in serum PSA with limited toxicity [63]. Similarly, a placebo-controlled, randomized phase III trial in patients with metastatic asymptomatic androgen-independent prostate cancer has reported statistically significant overall survival of 25.9 months with Sipuleucel-T, compared to 21.4 months with placebo [64]. Similarly, patients with PSA showing relapse following surgery or radiotherapy, may also benefit from immunotherapy with Sipuleucel-T [65].

CONCLUSION

Immunotherapy seems to be a promising novel approach in cancer therapy and may produce wonders when combined with chemotherapy and monoclonal antibodies [66-68]. The need of the hour is an ideal tumour vaccine that could induce active immunity in cancer patients, resulting in the rejection of specific tumour cells along with long-living immunologic

memory to protect against relapse. This is possible only if cancer vaccines could be designed based on the molecular biology of tumour cells taking into consideration the influence of immunotherapy on both malignant cells and immune system. However the major hurdles in developing cancer vaccines are identification of specific tumour antigens to target tumour cells and induce sufficient immune response to eradicate the tumour. Moreover attention has to be paid towards the escape mechanisms shown by the tumours to evade the host immune response.

Many preclinical studies with tumour-associated antigens, gene encoding tumour antigens and modified whole tumour cells have given the hope towards immunotherapy as an effective therapy for cancer [69-70]. Similarly, vaccines against hepatitis B-related liver cancer and HPV related cervical cancer also highlight the importance of population wide approaches for preventing cancers associated with infections. Moreover, cancer vaccines combined with monoclonal antibodies have shown synergism with enhanced efficacy and many such combinatorial strategies are being tested in cancer vaccine discovery and development. However to conclude, in spite of all the major advances in the medical field, cancer vaccines still remain as an experimental form of therapy and have a long way to go.

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