RECENT ADVANCES IN CANCER VACCINES: AN OVERVIEW

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Summary

The field of cancer vaccines is currently in an active state of clinical investigations. Human papilloma virus vaccines namely Gardasil and Cervarix have been approved as a prophylactic cancer vaccine. Oncophage (heat shock protein-peptide complex) was recently approved in Russia for a certain stage of kidney cancer; has been granted Orphan Drug status in Europe to treat brain cancer. Review on recent clinical trials of several different types of cancer vaccines was done mainly by using PubMed. There have been slow but substantial advances in peptide vaccines and dendritic cell-based vaccines with regard to both clinical responses and immunological markers. A personalized approach to boost immune responses, addition of chemotherapy to overcome robust cancers and changing of endpoints from tumour reduction to overall survival seem to be the three key elements for the development of therapeutic cancer vaccines.

Key words: Gardasil, Cervarix, Oncophage

The Immune System And Cancer

The immune system has the job of knowing the difference between normal cells and cancer cells. To keep us healthy, the immune system must be able to ignore or "tolerate" normal cells and recognize and attack abnormal ones. To the immune system, cancer cells differ from normal cells in very small, subtle ways as they also contain "SELF" antigens which mark them as body's own cells. Therefore, the immune system largely tolerates cancer cells rather than attacking them. Also cancer cells may not stimulate a strong immune response as they have developed ways to evade the immune system; for example some cancer cells shed certain molecules that make them invisible to the immune system.

Candidates for Vaccine Development

The major targets for vaccine development against cancer are the TUMOUR SPECIFIC ANTIGENS (TSAs). These TSAs mark and distinguish cancer cells thus making them more visible to the immune system. A number of promising cancer antigens, including NY-ESO-1, MAGE-3, NY-BR-1, SSX-2, NY-CO-58, and MELAN-A, are often found in certain cancer types, including melanoma, and breast, prostate, lung, colon, ovarian, and bladder carcinomas.

Types of Cancer Vaccines

A number of researches are being conducted to develop cancer vaccines that are either PROPHYLACTIC or THERAPEUTIC. Various approaches in developing a cancer vaccine are:

Microbial Vector Based Vaccines

These involve vectors such as Recombinant DNA, Bacteria, Viruses, etc. The HPV vaccines GARDASIL and CERVARIX, which are used as a prophylactic measure in cervical cancer are developed using rDNA technique [(1)]. In both the products the HPV capsid L_1 protein of the oncogenes E6 and E7 serves as a TSA. This protein is incorporated into a microbial vector (bacteria) and the latter is injected to the subject which boosts the immune system to produce large number of antibodies and CTLs.

Dendritic Cell Vaccines

More recently, vaccines composed of killed tumour cells or tumour antigens have been administered to patients and strategies for enhancing immune responses against the tumour are being developed. The major question for cancer immunotherapy is 'how can an effective anti-tumour CTL response be elicited'. The universal answer that has emerged is an effective anti-tumour CTL response requires that T cells be stimulated by specific antigen presenting cells that are called Dendritic cells (DC). DCs were first described as morphological distinct langerhans cells in the skin and have since been shown to be the most efficient APC for activation of naive T cells. The development of simple methods to isolate DC precursors from blood and the expansion of these cells *in vitro* to yield potent APCs have enabled their clinical use in cancer immunotherapy(21). Several approaches have been used to load DCs *ex*

vivo with tumour antigens. Antigen-loaded DCs are then given to patients in the hope that they will elicit a specific anti-tumour response. DCs can be loaded with (i) peptides eluted from MHC class I molecules; (ii) tumour-specific idiotype protein; (iii) RNA derived from neoplastic cells or by fusion of DC with tumour cells. Human clinical trials of tumour antigen loaded DC have been initiated for the treatment of B-cell lymphoma, prostate cancer melanoma and renal cell carcinoma. The Phase III clinical trials of DC-based vaccinations for asymptomatic metastatic HRPC patients conducted by the Dendrion Corporation (Seattle, WA, USA) demonstrated a significantly longer OS in treated patients when compared with those receiving the placebo. The results indicate that DC-based vaccination could be a promising treatment modality for various cancers, but multiple hurdles (reliable biomarkers, vaccine standardization and complicated protocols often resulting in conflicting outcomes, labour intensity, time consumption and high cost) must be cleared before the development of an affordable DC-based vaccination that can be used worldwide.

Peptide Vaccines:

HER-2/*neu* is an oncogene that is activated by gene amplification with the increased expression of a normal gene product. [(2)]As an over-expressed normal protein, HER-2/*neu* protein is an example of the recent "paradigm shift" in tumour immunology, which suggests that self-proteins can serve as tumour antigens. The most notable examples are in melanoma in which major proteins implicated in the tumour-specific immune response are non-mutated antigens expressed by some normal tissues, *e.g.,* MAGE and gp100. Thus, a current issue for the development of cancer vaccines is how best to induce T-cell immunity to "self" tumour antigens. Cancer vaccines targeting self tumour antigens must overcome immunological tolerance. Thus instead of vaccinating with the target proteins, the corresponding PEPTIDES offer an advantage of eliminating tolerance. At the 2008 meeting of American Society of Clinical Oncology, Becker et al. reported the results of a Phase I/II trial of a survivin-based peptide vaccine for therapy-resistant advanced cancer patients (n ¼ 79). Immune boosting was seen in 50% of the vaccinated patients. ORs were observed in six patients [7.6%, three complete response (CR) and three PR], and the patients showing CR, PR and
SD were restricted to immunological responders.

Heat Shock Protein vaccines:

The first autologous heat shock protein (HSP) vaccine introduced in clinical trials was Oncophage (HSP-peptide complex 96, HSPPC-96; Antigenics Inc., Levington, MA, USA). Since then, autologous HSP vaccines have been used for various types of cancer patients, but consistent clinical benefits have not yet been reported [(3)]. Twenty-one of 61 metastatic kidney cancer patients who received Oncophage vaccine responded to it with a median PFS time of 18 weeks. A Phase III trial of Oncophage for kidney cancer showed a 45% improvement in recurrent-free survival associated with Oncophage in a well-defined subgroup of earlier-stage (better-prognosis) patients, although a significant improvement was not observed in the overall patients' population [(4)]. Oncophage was recently (May 2008) approved in Russia for the treatment of kidney cancer patients at intermediate risk for disease recurrence. Oncophage was given the Orphan Drug Status by the US FDA in 2002. At the present time, there are conflicting opinions with regard to the clinical effectiveness of HSP-based vaccines [(3)]. Therefore, more clinical trials of HSP-based cancer vaccines will be needed before such vaccination can become a clinically effective treatment modality for all kidney cancer patients or other types of cancer patients.

Whole-Cell Vaccines

Canvaxin® is a polyvalent whole-cell vaccine developed at the John Wayne Cancer Institute in Santa Monica (CA, USA). It comprises three melanoma cell lines that express more than 20 characterized antigens. They include MAGE, tyrosinase TA-90, Lewis-X and MART-1. BCG is admixed as adjuvant. There were positive results from Phase II trials in patients with melanoma in 1996, in which 5-year OS was 39 versus 18%.[(5)] Responding patients demonstrated a cellular DTH response to some of the antigens, suggesting a correlation between immune response and clinical outcome. In 2002 a Phase III trial was set up in melanoma (stage III). It was meant to enrol more than 1100 patients and was carried out in 30 centres. Belagenpumatucel-L (Lucanix®) is a vaccine composed of four allogenic cell lines, which are originally derived from lung cancer patients and then engineered to block TGF-β. A randomized Phase II study based on the administration of different numbers of cells suggested a trend toward dose-related survival.[(6)] Cell-mediated responses to vaccine HLA antigens demonstrated a correlation trend in patients achieving stable disease or partial remission ($p = 0.086$)[(6)]. A Phase III study, researching this further, commenced in 2006.

DNA Vaccines and Anti—idiotype antibodies are the other promising approaches in cancer vaccine development.

Comparison of prophylactic HPV VLP vaccines

	Quadrivalent[a]	Bivalent[b]
Manufacturer	Merck Sharp & Dohme	GlaxoSmithKline
VLP types	6/11/16/18	16/18
Dose of L1 protein	20/40/40/20 µg	20/20 µg
Producer cells	*Saccharomyces cerevisiae*	*Trichoplusia ni*
Adjuvant	225 µg Aluminum hydroxyphosphate sulfate	500 µg Al(OH)3, 50 µg 3-O-deacylated-4'- monophosphoryl lipid A
Injection schedule in months	0, 2, 6 months	0, 1, 6 months

a: commercially designated as Gardasil™*; b*: commercially designated as Cervarix™.

A recombinant MAGE-3® vaccine was tested as adjuvant therapy in a multicenter, double-blind, randomized, placebo-controlled Phase II study in stage IB/II MAGE-3-positive, completely resected, NSCLC patients.

Recent advances of cancer vaccine trials using peptide vaccines and DC vaccines

Vaccine	Disease	Phase	Antigen	Pts N	CTL Increase	OR
Peptide vaccine	Advanced glioma	PI/PII	Personalize	25	67%	24%
	Advanced HRPC	PI/PII	Personalize	58	78%	24%
	Advanced NSCLC	PII	TERT	22	76%	0%
	Advanced BC	PI	TERT	19	68%	0%
	Advanced cancer	PI/PII	Survivin	79	50%	7.6%
	Advanced cancer	PI/PII	Personalize	211	66%	12.3%
	Resected melanoma	Random PI/PII	Mel. Pep.	60	63%	N.A
DC vaccine	Advanced NSCLC	PII	Multi. Pep	63	91%	3.2%
	Melanoma (Stage IV)	PII	Mel. Pep.	26	31%	3.8%
	Melanoma (Stage III/IV)	PII	Allo. tumours	20	55% (DTH)	0%
	Asymptomatic HRPC	Random PIII	PAP	82	NA	NA
	GBM	PII	Allo. tumours	32	53% NA	11%

Allo. tumours- allogeneic tumour cells; Auto. tumours- autologous tumour cells;BC- breast cancer;CTL-cytotoxic T lymphocytes;DTH-delayed-type hypersensitivity;GBM-glioblastoma multiforme; HRPC-hormone refractory prostate cancer;Mel. Pep.-melanocyte-derived peptide; Multi. Pep.- multiple melanoma-associated peptides; NA- not applicable; NSCLC-non-small cell lung cancer; OR- objective response; OS-overall survival; PAP- prostate acid phosphatase; PFS-progression-free survival; Pts N- patients number; TERT- telomerase reverse transcriptase.

Five year view

We anticipate a wave of cancer vaccines in market in another 5-6 years mainly due to the advances in clinical trials as discussed above. Even though there are promising results in phase I and II, there are challenges faced in decisive Phase III studies. The latter are important in establishing efficacy and supporting market authorisation.

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