available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Overcoming the hurdles of randomised clinical trials of therapeutic cancer vaccines

Tetsuro Sasada [a,d,*], Nobukazu Komatsu [a,b], Shigetaka Suekane [c,d], Akira Yamada [a,b], Masanori Noguchi [b,c], Kyogo Itoh [a,b]

[a] Department of Immunology and Immunotherapy, Kurume University School of Medicine, Fukuoka, Japan
[b] Division of Cancer Vaccine at the Research Center for Innovative Cancer Therapy, Kurume University School of Medicine, Fukuoka, Japan
[c] Department of Urology, Kurume University School of Medicine, Fukuoka, Japan
[d] Cancer Vaccine Center, Dana-Farber Cancer Institute, Boston, MA, USA

ARTICLE INFO

Article history:
Received 7 February 2010
Received in revised form 12 March 2010
Accepted 16 March 2010
Available online 21 April 2010

Keywords:
Cancer vaccine
Randomised clinical trial
Immune response
Personalisation

ABSTRACT

Most of the recent randomised clinical trials of therapeutic cancer vaccines have failed to demonstrate a meaningful therapeutic benefit to patients over existing treatments. Furthermore, some clinical trials have demonstrated a detrimental effect on patients, resulting in poorer outcomes. These unexpected results have shed light on several important issues to be solved for further development of cancer vaccines. As has been discussed with respect to the use of granulocyte–macrophage colony-stimulating factor (GM-SCF) as an adjuvant, the failures of clinical trials may be explained, in part, by a vaccine-specific adverse event, i.e. the induction of an 'inconvenient immune response' that inhibits pre-existing host immunity. This hypothesis may be supported by the fact that randomised trials of personalised peptide vaccines that were selected in consideration of pre-existing host immunities in individual patients resulted in clear benefit to patients. The development of reliable biomarkers for the selection of appropriate patients and vaccine antigens would thus be pivotal to prevent such vaccine-specific adverse events. This article discusses possible ways to overcome the hurdles of randomised clinical trials of therapeutic cancer vaccines based on a review of recently conducted clinical trials.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

The field of cancer vaccines has moved forward dramatically since 1991, when Boon and his colleagues reported their discovery of the first tumour-associated antigen.[1] Numerous tumour-associated antigens have been identified since that time, and some of them have been clinically tested with encouraging results in immunotherapy against patients with various types of cancer.[2–5] To date, however, no therapeutic cancer vaccines have been generally approved as a standard treatment for any type of cancer. Despite optimism and enthusiasm for cancer vaccine development, most of the randomised clinical trials designed to gain approval for clinical use have failed to demonstrate a meaningful therapeutic benefit to patients over existing treatments.[6,7] This situation has been further complicated by recent reports of several large

* *Corresponding author at:* Cancer Vaccine Center, Dana-Farber Cancer Institute, 77 Avenue Louis Pasteur, HIM 442, Boston, MA 02115, USA. Tel.: +1 617 582 8573; fax: +1 617 632 3351.
E-mail address: Tetsuro_Sasada@dfci.harvard.edu (T. Sasada).
0959-8049/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2010.03.013

clinical trials in which cancer vaccines sometimes had a detrimental effect on patients, resulting in poorer outcomes.[6–8] Such unexpected results have shed light on several important issues that must be resolved for future development of cancer vaccines. Although the FDA has recently published a guidance for industry to facilitate the marketing approval of these vaccines,[9] it has not fully addressed the issues raised by the failure of recent clinical trials, leading us to re-consider possible ways to overcome the hurdles of randomised clinical trials of therapeutic cancer vaccines.

2. Current status of cancer vaccine development

In the field of cancer vaccines, one of the most notable advances has been the recent development of two prophylactic vaccines against human papillomavirus (HPV) infection, Gardasil® (Merck & Co.) and Cervarix® (GlaxoSmithKline Biologicals), which contain L1 virus-like particles of high risk types of HPV.[10] In contrast to the great success of these preventive vaccines, there are still multiple hurdles to overcome for therapeutic cancer vaccines. Namely, most of the follow-up late-phase trials have failed to achieve their main endpoints (Table 1). For example, despite much hope and promising preliminary data, a large phase III clinical trial of GVAX immunotherapy for symptomatic metastatic prostate cancer (VITAL-2, Cell Genesys Inc.), which is comprised of two prostate tumour cell lines secreting granulocyte–macrophage colony-stimulating factor (GM-SCF), were prematurely terminated due to an imbalance in deaths between the treatment and control arms of the study [hazard ratio (HR) = 1.4; $P = 0.02$; median overall survival, 12.4 months (treatment) versus 14.8 months (control)].[11] Another phase III randomised trial with GVAX immunotherapy for asymptomatic metastatic prostate cancer (VITAL-1, Cell Genesys Inc.) was also terminated based on the result of a futility analysis conducted at the company's request.[11] In addition, two randomised clinical trials of soluble protein idiotypic vaccination for follicular lymphoma have recently failed to achieve clinical benefits, although these 'personalised' vaccines got much attention. Of note, one of these studies showed a statistically significant difference in the time to progression (TTP) in favour of the patients treated with the control product [HR = 1.384; $P = 0.019$; TTP, 9.0 months (treatment) versus 12.6 months (control)].[12] Although a detailed analysis of these negative results has been awaited to help identify factors that are related to clinical benefit of idiotypic vaccination, the failure of these clinical trials is suggested to be due to the defect in clinical trial designs rather than due to the properties of vaccines themselves.[12]

Despite the failure of most of the recent randomised trials, there have been some encouraging advances. The phase III trial of dendritic cell (DC)-based vaccine (Provenge®, Dendrion Corporation) loaded with a recombinant fusion protein containing prostatic acid phosphatase (PAP) and GM-CSF has recently demonstrated a significantly longer overall survival in asymptomatic metastatic prostate cancer patients.[7] This result has been submitted to the FDA for approval of this product as the first therapeutic cancer vaccine in the United States. However, before this treatment modality can be made clinically available worldwide, multiple hurdles must be overcome, including the complicated protocols and the extremely high money, labour and time costs involved in the preparation of standardised vaccines. In addition, in April 2008, an autologous, tumour-derived heat-shock protein (glycoprotein 96)-peptide complex (vitespen; Oncophage®, Antigenics Inc.) became the first cancer vaccine approved in Russia for use as an adjuvant treatment for renal cell carcinoma patients with intermediate risk of disease recurrence.[7] However, post-marketing studies will still be needed to confirm its consistent clinical benefits, because this product showed no advantage in patient survival in the randomised phase III trials of renal cell carcinoma and melanoma.[7]

Recent early-phase clinical trials have also demonstrated significant advances in therapeutic peptide vaccines.[4,5,13–17] For example, therapeutic HPV vaccines have been reported to be effective for people with high risk of developing HPV-related cancers. Melief and his colleagues showed that a vaccine composed of a synthetic long peptide pool derived from HPV-16 E6/E7 oncoproteins successfully induced HPV-specific immune responses and caused measurable regression of HPV-infected precancerous genital lesions in a majority (79%) of patients.[13] In addition to these antigens derived from oncogenic infectious agents that are recognised as foreign by the host immune system, vaccination with 'self'-antigen peptides also has shown substantial progress. In

Table 1 – Randomised clinical trials of cancer vaccines with negative results.

Product	Immunogen	Target cancer	Disease status	Company (organisation)
Melacine	Allogeneic cell lysate	Melanoma	Adjuvant	Corixa
Canvaxin	Allogeneic cells	Melanoma	Metastasis, adjuvant	CancerVax
PANVAC-VF	CEA, MUC-1	Pancreas cancer	Metastasis	Therion Biologics
Oncophage	Vitespen, heat-shock protein	Renal cell cancer	Metastasis, adjuvant	Antigenics
Oncophage	Vitespen, heat-shock protein	Melanoma	Metastasis	Antigenics
GM2-KLH21	GM2-KLH21	Melanoma	Adjuvant	EORTC[a]
TroVax	MVA-5T4	Renal cell cancer	Adjuvant	Oxford BioMedica
MyVax	Id-KLH + GM-CSF	Non-Hodgkin's lymphoma	Adjuvant	Genitope
FavId	Id-KLH + GM-CSF	Non-Hodgkin's lymphoma	Adjuvant	Favrille
GVAX	GM-CSF producing cells	Prostate cancer	Metastasis, refractory	Cell Genesys
Theratope	sTn-KLH	Beast cancer	Metastasis	Oncothyreon

[a] EORTC: European Organisation for Research and Treatment of Cancer.

Download English Version:

https://daneshyari.com/en/article/2123392

Download Persian Version:

https://daneshyari.com/article/2123392

Daneshyari.com