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Vaccine immunotherapy in lung cancer: Clinical experience and future directions

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ABSTRACT

Lung cancer remains the most common cause of cancer-related deaths in the United States, with SEER data showing lung cancer accounting for 29% of all male-related cancer mortality and 26% of all female-related mortality. Patients with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) who have localized disease both have 5-year survival rates of 52.2%, whereas patients with metastatic disease have 5-year survival rates of only 3.7%. Traditional anti-cancer therapies (surgery, radiotherapy, and chemotherapy) have limited effectiveness in curbing progression. However, advances in immunology and molecular biology in the past two decades have resulted in improved prognosis for those with SCLC and NSCLC, although novel therapies are still needed to make significant improvements in median overall and progression-free survival rates. Notable progress on the importance of tumor immunology has included work on immune surveillance, antigenic targets, and immune checkpoints. Immunotherapies, including vaccines, which can induce antitumor responses by harnessing the power of the immune system, may help to fill this void, and the cancer vaccine continues to be studied as adjunctive therapy. Here, we review recently reported results from clinical trials as well as the possible future roles of vaccine therapy in the treatment of SCLC and NSCLC patients.

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1. Introduction

Lung cancer remains the most common cause of cancer-related deaths in the United States. Based on estimates published by the Surveillance, Epidemiology, and End Results (SEER) database, 160,340 American men and women died of a lung or bronchus malignancy in 2012. Deaths attributable to lung cancer accounted for 29% of all male-related cancer mortality and 26% of all female-related mortality (National Institutes of Health, 2012a). At best, patients with localized disease have a 5-year survival rate of 52.2%, whereas patients with metastatic disease have a 5-year survival rate of only 3.7% (National Institutes of Health, 2012b). These survival rates include patients with both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

Although significant advances have been made in the treatment of NSCLC with the use of molecular targeted therapies such as erlotinib and crizotinib, median overall survival (OS) for patients with advanced NSCLC (stage IIIB or IV) treated with epidermal growth factor receptor (EGFR)-targeted therapy averages only 24 months (Jackman et al.,

Abbreviations: ATRA, all-trans retinoic acid; BSC, best supportive care; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen 4; DFS, disease-free survival; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; GAR, good antibody responder; HPV, human papilloma virus; HR, hazard ratio; IL, interleukin; LASEP3, lung cancer-associated serum protein 3; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer; TGF-β, transforming growth factor β.

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2009). Thus, novel therapies are needed to make significant improvements in median OS and progression-free survival (PFS) for both SCLC and NSCLC. There has been notable progress in the realm of tumor immunology such as immune surveillance, antigenic targets, and immune checkpoints. Immunotherapies, including vaccines, which by exploiting the immune system can induce antitumor responses, represent an alternate strategy that may help to fill this void. Antitumor responses can be generated by administering a vaccine containing a unique allogeneic tumor antigen to individuals in order to stimulate humoral immune response against the specific antigen. To prime the immune system and activate those cytotoxic T-cells needed to generate the relevant immune responses to the tumor of interest, vaccines have evolved to harbor more specific immunogenic tumor-associated antigens of interest as a source of a stimulant. Cancer vaccines can utilize different strategies for source of tumor antigen targets, including but not limited to whole tumor cells, DNA bearing viral vectors, proteins, or peptides (Table 1). When coupled with an adjuvant, the antigen-specific immune response can be enhanced. As an example, the prophylactic vaccine against human papilloma virus (HPV) types 16 and 18 is formulated with MPL (monophosphoryl lipid A), a toll-like receptor-4 adjuvant shown to promote immune response.

Vaccines have been utilized for both cancer prevention and treatment; as examples, the hepatitis B vaccine and recombinant HPV vaccine (Gardasil and Cervarix) both prevent infection with cancer-causing viruses. The approved vaccines for cancer treatment and prevention have included BCG vaccine for non-muscle invasive bladder cancer (which induces a non-specific upregulated immune response) and the sipuleucel-T for hormone-refractory prostate cancer (an autologous tumor cell vaccination). The ultimate goals of vaccine therapy are to harness the inherent inducibility and specificity of the immune system to produce long-lasting, active memory, which in turn would yield faster and more robust responses to re-exposure.

Table 1
Summary of cancer vaccines.

Type of vaccine	Preparation	Examples
Preventative vaccines	Prevent the development of specific cancers by preventing causative infection	Gardasil Cervarix Hepatitis B
Treatment vaccines	Boost the immune system to attack cancer cells	
Allogeneic vaccines	Non-self cancer cells grown in a lab and treated to make them a target to the immune system, then injected into a patient to cause an immune response	GVAX (+GM-CSF) BLP-25 (anti-MUC1) Belagenpumatucel-L TG4010 CIMAvax EGF NY-ESO GM.CD40L-CCL21
Autologous vaccine	Cells from a patient's own tumor are extracted and treated to make them an immune target, then injected back into the body	Adeno-CD40L BCG INGN-225
Dendritic cell vaccine (subset of autologous vaccines)	Immune cells removed from a patient, then exposed to cancer cells or cancer antigens and chemokines, then injected back into the patient to provoke an immune response	Sipuleucel-T Glioma peptides rF-CEA-MUC1-TRICOM (panvac-DC)
DNA vaccines	Patient is vaccinated with a preparation containing plasmids, which prompt cells to produce tumor antigens, which then signal the immune cells to respond toward similar antigens on existing cancer cells	Synchotrope MA2M plasmid DNA vaccine ZYC101
Antigen vaccines	Made from parts of cancer cells, either proteins or peptides, instead of whole tumor cells. These are delivered as a vaccine alone, coupled with carriers, or in combination with immune-stimulating molecules	MUC-1 (stimuvax) NY-ESO-1 GP-100 MAGE-A3 INGN-225
Vector-based vaccines	Vectors (bacteria, viruses, yeast) used to introduce cancer-related antigen or proteins and thus induce an immune response	PSA-TRICOM (prostvac) PANVAC-VF Listeria-mesothelin Adeno-CEA

Until recently, the experience with vaccine therapy in lung cancer has been discouraging; however, there have been a number of promising advances in the treatment of both NSCLC and SCLC. Herein, we describe the clinical experience with vaccine therapy in each disease model. Additionally, a summary of vaccine trials in both NSCLC and SCLC can be seen in Tables 2 and 3, respectively.

2. Non-small cell lung cancer

This section reviews recent studies of allogeneic cancer vaccines that are the subject of phase III clinical trials: BLP-25 anti-MUC1, belagenpumatucel-L, TG4010 (modified virus of Ankara–mucin 1 [MUC1]–interleukin 2 [IL-2]), CIMAvax epidermal growth factor (EGF), melanoma antigen encoding gene A3 (MAGEA3), GM.CD40L, and NYESO.

2.1. BLP-25 (anti-Ankara–mucin 1)

MUC1 is a mucinous glycoprotein associated with cellular transformation, can confer resistance to cytotoxic agents, and is overexpressed in many human malignancies. High levels of serum MUC1 are associated with poor prognosis and immunosuppression in patients with advanced adenocarcinoma (Reddish, M.G., Poppema, Berg, & Longenecker, 1996). As shown in preclinical studies, BLP-25, a liposomal peptide vaccine that targets the exposed core peptide of MUC1, induced a cellular immune response characterized by antigen-specific T-cell proliferation and production of interferon-gamma (Agrawal, K.M., Reddish, & Longenecker, 1998). BLP-25 was initially evaluated in a phase I trial in stage IIIB/IV NSCLC patients (Palmer et al., 2001), which was delivered via two subcutaneous injections to the upper arm 3 days after infusion of cyclophosphamide 300 mg/m^2 (given to inhibit suppressor T cells). The most common reactions were grade 1/2 injection-site erythema (9 patients), grade 1/2 liver enzyme elevations (6 patients), myalgias/arthralgias (5 patients), and fatigue (5 patients). One patient from each of the two dose arms developed grade 3 lymphopenia. The study also quantified cytotoxic T-cell responses; of 12 patients, 5 demonstrated in vitro cytotoxic T-cell responses when exposed to MUC1 antigen. However, none demonstrated a detectable humoral response. The median OS between the two dose arms was not statistically significant due to the underpowered nature of the analysis but favored the group receiving the highest vaccine dose. At week 13, 4 patients achieved stable disease and were eligible to receive additional vaccine treatments on a compassionate basis, whereas the remaining 8 patients showed evidence of disease progression.

Building on these data, a phase IIB study was conducted across 17 sites in the United Kingdom and Canada and initially published in 2005 (Butts et al., 2005) and later updated in 2011. This study randomized 171 patients with stage IIIB or IV NSCLC who experienced "stable disease or an objective response" at the conclusion of first-line chemotherapy to receive best supportive care (BSC) or the BLP-25 vaccine. BLP-25 was administered in a manner similar to that in the phase I study. The primary endpoint was survival measured from the day of randomization to the date of death. After a median follow-up of 26 months, the median OS for patients who received BLP-25 did not differ statistically from that for patients who received BSC (17.4 months and 13 months, respectively; hazard ratio [HR] = 0.739; 95% confidence interval [CI]: 0.509–1.073; P = 0.112). For patients with locoregional disease (n = 65), the OS approached statistical significance, with a 2-year survival rate of 60% in the BLP-25 arm and 36.7% in the BSC group. The median OS in the locoregional BLP-25 group was not reached at the conclusion of the initial study. Cytotoxic T-lymphocyte responses were measured in patients receiving the BLP-25 vaccine. Of 78 patients,