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Therapeutic Cancer Vaccines: The Latest Advancement in Targeted Therapy

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Abstract

Therapeutic cancer vaccines represent an emerging therapeutic modality that may play a more prominent role in cancer treatment in the future. Therapeutic cancer vaccines are designed to generate a targeted, immune-mediated antitumor response. There are two main types of therapeutic vaccines: patient-specific (generated either from a patient's own cells or tumor) and patient-nonspecific, where a peptide- or vector-based vaccine induces an immune response *in vivo* against specific tumor-associated antigens. Studies are currently underway to investigate methods to enhance vaccine strategies, including combinations with standard anticancer therapies or immune-modulating agents. Cancer vaccines are usually well tolerated, with minimal toxicity compared to chemotherapy. This review summarizes selected therapeutic cancer vaccines in late clinical development.

Keywords

therapeutic cancer vaccines; immunotherapy; combination therapy; anti-CTLA-4

INTRODUCTION

Although therapeutic cancer vaccines have been the subject of preclinical and clinical investigation for many years, it was 2010, before one of these agents received approval from the United States Food and Drug Administration (US FDA).¹ Currently, many more such vaccines with different approaches to treating cancer are in clinical development. As medical oncologists become more familiar with immune-based strategies, these cancer vaccines may play a more prominent role in treating patients with various types of malignancies.

The fundamental goal of cancer immunotherapy is to induce a targeted immune responses against cancer cells.² Nonspecific types of immunotherapy such as interferon-alpha (IFN- α) and interleukin-2 (IL-2) can induce a generalized immunologic response that may have an antitumor effect in a minority of patients. Ideally, therapeutic cancer vaccines can induce a focused antitumor immune response by targeting specific tumor-associated antigens (TAAs) through T-cell stimulation. Human cytotoxic T cells are able to recognize 9- to 14-mer antigenic peptides expressed within the major histocompatibility complex (MHC) on the surface of all cells. These peptides are derived from endogenously expressed proteins,

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including TAAs that are processed by proteases within cells. When appropriately activated, T cells can detect specific TAAs with the MHC and initiate targeted, immune-mediated cell killing.^{3,4}

The ideal TAA is specific to, or overexpressed on, the surface of cancer cells. Although vaccines generally focus on a specific TAA, the subsequent immune response may not be limited to the targeted TAA. Clinical data indicate that vaccine-activated immune cells that are exposed to lysed cancer cells may detect additional TAAs not contained in the vaccine, and ultimately target tumor cells through these secondary antigens. This process is known as antigen cascade or antigen spreading.⁵

To be effective, a therapeutic cancer vaccine must achieve two goals. First, the vaccine must stimulate specific immune responses against the appropriate target. Second, the immune responses must be sufficient to overcome immunosuppressive mechanisms that can be employed by tumors.⁶ There are several immunologic strategies for accomplishing these goals, two of which are featured in this review. Autologous vaccines are generated from a patient's own cells or tumor. These patient-specific vaccines are generated *ex vivo* and their production is generally labor-intensive. Another approach is patient-nonspecific, where a peptide- or vector-based vaccine is designed to deliver a TAA to the immune system *in vivo*, allowing for immune activation within the patient.⁷ Strategies for enabling cancer vaccines to overcome immunosuppressive barriers to generate an immune response are also discussed in this review. Regardless of the specific approach, cancer vaccines are much less toxic than either chemotherapy or targeted molecular inhibitors.

This review will focus on selected therapeutic cancer vaccines in late clinical development in diseases such as prostate cancer, non-small cell lung cancer, and non-Hodgkin's lymphoma. It will also examine some of the immune parameters currently being employed.

PROSTATE CANCER

In Western countries, prostate cancer is the most common cancer in men and ranks third in terms of mortality.⁸ The dearth of curative therapies for recurrent prostate cancer that no longer responds to hormonal agents has prompted research into novel treatment approaches. Immunotherapy is particularly promising, since prostate cancer is an indolent disease that may allow time for the immune system to mount a meaningful immunologic response. Since the prostate is a nonessential organ, targeting prostate cancer-associated antigens is unlikely to have significant negative clinical effects. In addition, several TAAs can be targeted to promote prostate tumor-cell injury or apoptosis, including prostate-specific antigen (PSA),⁹ prostate-specific membrane antigen (PSMA),¹⁰ prostatic acid phosphatase (PAP),¹¹ T-cell receptor gamma chain alternating reading frame protein (TARP),¹² and new gene expressed in prostate (NGEP).¹³

Sipuleucel-T (Provenge™)

Sipuleucel-T is a cellular product that is manufactured for each patient after harvesting peripheral blood mononuclear cells, including antigen-presenting cells (APCs). These cells are then exposed *ex vivo* to a recombinant protein consisting of GM-CSF fused to PAP (PA2024) in a process designed to activate them. After processing, the cells are reinfused into the patient, with the goal of generating an immune response against PAP.¹⁴ Initial phase I and II trials have shown that treatment is well tolerated, with no dose-limiting toxicities.¹⁵⁻¹⁷

The IMPACT trial (IMmunotherapy for Prostate AdenoCarcinoma Treatment), a phase III, randomized, double-blind, placebo-controlled, multicenter study, enrolled 512 men with

minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Patients were randomized 2:1 to receive sipuleucel-T (n = 341) or placebo (n = 171) every 2 weeks for 3 treatments. The primary endpoint was overall survival (OS). Sipuleucel-T prolonged median OS by 4.1 months compared to placebo (25.8 vs. 21.7 months) and reduced the risk of death from any cause by 22.5% (HR 0.775; $P = 0.032$). The vaccine was generally well tolerated, with the most frequent side effects being chills (54.1%), pyrexia (29.3%), headache (16%), flu-like symptoms (9.8%), myalgia (9.8%), hypertension (7.4%), and hyperhydrosis (5.3%).¹⁸ Based on the IMPACT data, the US FDA approved sipuleucel-T for use in minimally symptomatic mCRPC, making it the first therapeutic cancer vaccine approved in the United States.¹

The IMPACT trial evaluated immune activity in the form of antibody response and T-cell proliferation. Antibody responses (defined as titers > 400 via ELISA) were detected in 66.2% of 151 evaluated sipuleucel-T-treated patients, compared to 2.9% of 70 patients in the placebo arm. Antibodies to PAP were detected in 28.5% of sipuleucel-T-treated patients, compared to 1.4% of placebo-treated patients. These antibody titers were associated with improved survival outcomes for patients with titers < 400 to PA2024 ($P < 0.001$) and PAP ($P = 0.08$). Increased levels of T-cell proliferation in response to these two antigens were also detected; however, there was no association with improved survival.

PSA-TRICOM (PROSTVAC™)

PSA-TRICOM is a vector-based vaccine that uses recombinant poxviruses to initiate an immune response against PSA-expressing cells. The vaccine also contains transgenes for three T-cell costimulatory molecules to enhance T-cell activation: B7.1 (CD80), lymphocyte function-associated antigen 3 (LFA-3), and intracellular adhesion molecule 1 (ICAM-1), known as TRICOM.¹⁹ The vaccine is administered by subcutaneous injection, which leads to poxviral infection of APCs. The vectors then enter the cellular cytoplasm, where the transgenes for PSA and the costimulatory molecules are transcribed. The resulting products are processed by the APCs and displayed in the MHC on their surfaces. Subsequently, APCs activate CTLs through recognition of the TAA within the MHC, and the CTLs are activated to lyse tumor cells expressing PSA.²⁰

A phase I trial of PSA-TRICOM demonstrated safety, with local injection-site reaction as the most common adverse event.²¹ A subsequent randomized, placebo-controlled, phase II study of PSA-TRICOM in patients with minimally symptomatic mCRPC was recently reported.¹⁹ This study randomized patients 2:1 to receive either PSA-TRICOM (n = 84) or placebo (n = 41). The primary endpoint was progression-free survival (PFS), with a secondary endpoint of OS. There was no difference in PFS between the 2 groups (3.8 vs. 3.7 months). However, at 3 years post-study, PSA-TRICOM patients had greater OS, with 25/82 (30%) patients alive vs. 7/40 (17%) controls, longer median survival by 8.5 months (25.1 vs. 16.6 months for controls), an estimated HR of 0.56 (95% CI, 0.37 to 0.85), and stratified log-rank $P = 0.0061$. In a smaller trial in a similar patient population at the National Cancer Institute, PSA-TRICOM generated PSA-specific T-cell responses (via ELISPOT assay) within 3 months in 12 of 29 evaluable patients. Furthermore, patients with the greatest magnitude of antigen-specific immune responses had the most favorable survival outcomes.²² These promising data will be evaluated with a larger phase III study that will begin in late 2010 or early 2011.²³

NON-SMALL CELL LUNG CANCER

Carcinoma of the lung is the leading cause of cancer death worldwide, with non-small cell lung cancer (NSCLC) constituting about 85% of all new diagnoses.⁸ Patients with resectable disease may be cured by surgery or surgery with adjuvant chemotherapy. Local control can

be achieved with radiation therapy in a large number of patients with unresectable disease, but only a small number of patients are cured. Patients with locally advanced, unresectable disease may have long-term survival with radiation therapy combined with chemotherapy. Patients with advanced metastatic disease may have improved survival and palliation of symptoms with chemotherapy. Despite decades of research, no specific, active cancer vaccine has been FDA-approved for NSCLC therapy; nevertheless, vaccine therapy has recently re-emerged as a potential therapeutic approach.

L-BLP25 (Stimuvax™)

L-BLP25 is an investigational therapeutic cancer vaccine designed to induce an immune response against cancer cells that express mucin 1 (MUC1). L-BLP25 is a lyophilized preparation consisting of BLP25 lipopeptide, the immunoadjuvant monophosphoryl lipid A, and three types of lipids (cholesterol, dimyristoylphosphatidylglycerol, and dipalmitoylphosphatidylcholine), forming an immunogenic liposomal product.²⁴ MUC1 is a highly glycosylated type 1 transmembrane protein normally found on the apical surface of mucin-secreting epithelial cells in breast, prostate, lung, pancreas, stomach, and ovarian tissue. In tumor tissue, it is associated with reduced apoptosis, malignant transformation, and anchorage-independent cell growth.²⁵ MUC1 is a potential target for vaccine therapy because of its overexpression or aberrant glycosylation in tumors compared with normal tissue.^{26,27}

Butts et al. published the results of a randomized phase IIB trial that enrolled patients with stage IIIB or IV NSCLC who had responded to, or remained stable on, any standard first-line therapy. Patients were randomized to receive either L-BLP25 plus best supportive care (88 patients) or best supportive care alone (83 patients). Patients in the L-BLP25 arm received a single intravenous dose of 300 mg/m² cyclophosphamide, followed by 8 weekly subcutaneous immunizations with L-BLP25 (1,000 µg). Maintenance immunizations were given at 6-week intervals. (Cyclophosphamide at such a low dose is given to deplete regulatory immune cells and does not have significant cytotoxic potential.) The median OS was 17.4 months for patients receiving vaccine vs. 13.0 months for patients receiving best supportive care alone ($P = 0.112$). No severe toxicities were reported. T-cell proliferation assays indicated immune responses in 78 of 88 (88.6%) L-BLP25-treated patients. Sixteen patients who had MUC1-specific T-cell proliferation responses had a median OS of 27.6 months compared to 16.7 months for patients with no MUC1-specific T-cell proliferation response.²⁸ A subgroup analysis suggested that the greatest survival benefit was seen in patients with stage IIIB locoregional disease (adjusted HR = 0.524; 95% CI, 0.261 to 1.052; $P = 0.069$).²⁸ A subsequent study of L-BLP25 evaluated 22 patients with stage III NSCLC who had been treated with front-line chemotherapy. The median OS in this study was similar to the subgroup analysis from the randomized phase IIB study at a median follow-up of 53 months.²⁹

Based on these data, an international, randomized phase III trial of L-BLP25 vs. placebo was initiated in patients with stage III NSCLC. The START trial (Stimulating Targeted Antigenic Responses to NSCLC) is designed to randomize 1,322 patients with stage IIIA and IIIB disease without progression after standard chemotherapy and radiation, to L-BLP25 vs. placebo given sequentially or concurrently, with OS as the main endpoint.³⁰ A second, smaller trial will enroll over 400 Asian patients with the same stage of disease in order to explore any differential effects on that population.³¹

MAGE-A3 Vaccine

The melanoma-associated antigen (MAGE) is a promising candidate for targeted immunotherapy because it is expressed in cancer cells but not in normal tissue.³² The

MAGE-A3 gene family codes for an antigenic nonapeptide that is recognized by cytolytic T cells on the human leukocyte antigen (HLA)-A1 molecule. It is expressed in about 35% of NSCLC patients and may be associated with poor prognosis.³³ The MAGE-A3 vaccine was developed to treat patients who carry the HLA-A1 allele and express MAGE-A3 in their primary tumors.³⁴

In a randomized phase II trial, patients with completely resected, MAGE-A3-positive, stage IB/II NSCLC were assigned to receive postoperative MAGE-A3 vaccine or placebo. Patients were given one intramuscular injection every 3 weeks (total of 5), then once every 3 months (total of 8). The primary endpoint was disease-free interval (DFI); other endpoints were safety, disease-free survival (DFS), and OS. Of 1,089 lung cancer resection specimens evaluated for MAGE-A3 expression, 363 were positive. Of these, 182 patients (122 stage IB, 60 stage II) were randomized. In total, 1,214 doses of MAGE-A3 vaccine were administered, with grade 3 to 4 side effects reported in 9.6% of cases. Only 3 grade 3 events were possibly related to the vaccine. With a median follow-up of 28 months, 30.6% of patients in the vaccine arm had recurring disease vs. 43.3% of patients in the placebo arm. However, none of the outcome endpoints reached statistical significance, with respective HRs for DFI, DFS, and OS in favor of the MAGE-A3 group: 0.74 (95% CI, 0.44 to 1.20; $P = 0.107$), 0.73 (95% CI, 0.45 to 1.16; $P = 0.093$), and 0.66 (95% CI, 0.36 to 1.20; $P = 0.088$).³⁵ MAGRIT (MAGE-A3 as Adjuvant non-small cell lung cancer ImmunoTherapy), an ongoing randomized phase III trial, is enrolling 2,270 resected MAGE-A3-positive patients randomized to either vaccine or placebo, with DFS as the primary endpoint.³⁶

NON-HODGKIN'S LYMPHOMA

There are approximately 65,000 new cases of non-Hodgkin's lymphoma diagnosed each year in the US, with follicular lymphoma comprising approximately 30% of all cases. Even with aggressive treatment with chemotherapy and monoclonal antibodies, follicular lymphoma is almost invariably fatal, in spite of its indolent course. The median relapse time for follicular lymphoma is 3 years, with 90% tumor-related mortality within 7 years of diagnosis.³⁷ The surface immunoglobulin (Ig) on each B-cell lymphoma cell has unique portions (idiotypes) that can be recognized by the immune system, making them potential targets for vaccine.

BiovaxID

The clonal immunoglobulin molecule expressed on the surface of B-cell malignancies, idiotype (ID), can function as a tumor-specific antigen. BiovaxID is a patient-specific therapeutic cancer vaccine composed of the tumor ID conjugated to the carrier protein keyhole limpet hemocyanin (KLH).

Initial studies demonstrated promising results. After standard chemotherapy, 41 patients with non-Hodgkin's B-cell lymphoma received a series of injections with a vaccine consisting of tumor Ig protein coupled to KLH and emulsified in an immunologic adjuvant. Prior to vaccine treatment, 32 patients were in their first remission and 9 were in subsequent remissions. The median follow-up for all patients is 7.3 years from diagnosis and 5.3 years from the last chemotherapy treatment before vaccine administration. Twenty patients (49%) generated specific immune responses against the IDs of their tumor Ig. Two patients who had residual disease experienced complete tumor regression associated with the development of these immune responses. All 20 patients who mounted an anti-ID immune response had significantly prolonged median duration of PFS and OS compared to patients who did not mount an immune response. Analysis of the 32 first-remission patients also showed an improved clinical outcome for patients who mounted a specific immune response

compared to those who did not (PFS, 7.9 vs. 1.3 years; $P = 0.0001$; median OS from time of last chemotherapy not yet reached vs. 7 years; $P = 0.04$).³⁸

Based on these phase II results, a subsequent randomized, double-blind, placebo-controlled, multicenter phase III study of a patient-specific autologous tumor-derived ID vaccine was initiated in advanced-stage, untreated follicular lymphoma patients who achieved a complete response (CR) or complete response unconfirmed (CRu) after chemotherapy with PACE (prednisone, doxorubicin, cyclophosphamide, etoposide). Patients were stratified by International Prognostic Index risk group and randomized 2:1 to receive either vaccination with ID-KLH/GM-CSF or control (KLH/GM-CSF). The primary endpoint was DFS. Of the 234 patients enrolled, 177 (76%) achieved CR/CRu and were randomized. Of these 177 randomized patients, 117 maintained CR/CRu 6 months per protocol requirement, and then received 1 dose of vaccine; 55 relapsed before vaccination. Patients who received 1 dose of vaccine constituted the modified intent-to-treat population for determination of efficacy. Seventy-six patients received ID-KLH/GM-CSF and 41 received the control (KLH/GM-CSF). At a median follow-up of 56.6 months (range 12.6 to 89.3 months), median time to relapse after randomization for the ID-KLH/GM-CSF arm was 44.2 months vs. 30.6 months for the control arm ($P = 0.045$; HR = 1.6),³⁹ suggesting possible clinical benefit from the ID-derived vaccine.

COMBINATION THERAPY

Therapeutic cancer vaccines as monotherapy have demonstrated varying levels of clinical efficacy in clinical trials; however, their ultimate role may be in combination with standard therapeutics. Emerging data suggest that the immune-mediated tumor-cell killing induced by cancer vaccines can be augmented by conventional anticancer therapies.³⁰ Standard treatments may up-regulate MHC molecules, enhance TAA expression, and induce apoptosis by increasing the expression of cell-death receptors such as TNF receptor, TNF-related ligand receptors, and Fas.⁴⁰ Regulators of immune response, such as certain cytokines and immune regulatory cells, may decrease the immune response that can be generated against a tumor.⁴¹⁻⁴⁵ Agents that suppress these barriers to immune activation may thus enhance immune response to cancer vaccines. This strategy is demonstrated by the L-BLP25 vaccine discussed above, which employs low-dose cyclophosphamide to deplete regulatory T cells prior to vaccine administration.²⁴ Other strategies employing novel immunotherapeutics are also under investigation.

IPILIMUMAB

Ipilimumab is a fully human antibody that binds cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a molecule on T cells that is believed to play a critical role in down-regulating immune responses. Within hours after T-cell activation, CTLA-4 expression and subsequent binding with APCs results in down-regulation of the T-cell mediated immune response. The important regulatory role of CTLA-4 is highlighted in CTLA-4 knockout mice, who rapidly succumb to multi-organ failure resulting from infiltrating autoreactive T cells.⁴⁶ A CTLA-4 blockade may prevent CTLA-4 binding, potentially prolonging and enhancing vaccine-initiated immune activity against tumors.⁴⁷⁻⁴⁹

CTLA-4 blockade has been evaluated in several malignancies, but the most mature data come from metastatic melanoma. A phase III study⁵⁰ enrolled patients with unresectable advanced (stage 3/4) melanoma, randomized to 3 treatment groups in a 1:3:1 ratio: ipilimumab plus placebo (n = 137), ipilimumab plus glycoprotein 100 (gp100) melanoma antigen vaccine (n = 403), and gp100 vaccine plus placebo (n = 136). In this study, gp100, an older peptide-based vaccine, was used as an active immunologic control. The primary endpoint was OS. Patients receiving ipilimumab plus gp100 had a median survival of 10

months, compared with 6.4 months for patients receiving the vaccine alone (HR for death, 0.68; $P < 0.001$). The median OS with ipilimumab alone was 10.1 months (HR for death in comparison with gp100 alone, 0.66; $P = 0.003$).

The effects of ipilimumab on immune regulatory mechanisms can potentially enhance the effects of a therapeutic cancer vaccine. A previous study combined a whole tumor cell vaccine with ipilimumab in mCRPC. In addition to the injection-site reactions and flu-like symptoms normally seen with the vaccine, the combination was also associated with immune-mediated side effects, notably hypophysitis, in 5 of 6 patients treated with the highest dose level of ipilimumab (5 mg/kg). PSA declines $> 50\%$ were reported in these 5 patients (durations 6.7 to 23.1 months). In addition, 4 patients had stable bone scans for 3 months. Immunologic responses in the form of dendritic-cell and T-cell activation were also reported at the higher dose levels. After these initial findings are analyzed, another cohort of patients will be enrolled to further assess safety and efficacy.^{51,52}

Another phase I study combined escalating doses of ipilimumab with PSA-TRICOM in 30 patients with mCRPC. The doses of ipilimumab were 1, 3, 5, and 10 mg/kg, with an expansion cohort of 15 patients at the 10 mg/kg dose level. Again, immune-mediated adverse events were reported, but there was no clear association with response. The median survival was 31.8 months, with a 74% survival probability at 24 months.⁵³ These data compare favorably with previous studies of PSA-TRICOM alone that yielded a median survival of approximately 26 months, suggesting that the combination of vaccine and CTLA-4 blockade warrants further investigation.^{19,22}

BELAGENPUMATUCEL-L (LUCANIX™)

Transforming growth factor $\beta 2$ (TGF- $\beta 2$) suppresses natural killer (NK) cells and activates killer cells and dendritic cells. It has been identified as a poor prognostic factor in NSCLC. Belagenpumatucel-L is a novel vaccine prepared by transfecting allogeneic cancer cells with a plasmid containing a TGF- $\beta 2$ antisense transgene, expanding the cells, and then irradiating and freezing them. Upon administration, this agent generates an immune response against cancer cells, resulting in decreased tumor-cell proliferation. Vaccine immunogenicity may be potentiated by the suppression of tumor TGF- $\beta 2$ production by the antisense RNA expressed by the vaccine plasmid TGF- $\beta 2$ antisense transgene.⁵⁴

A phase II study involving 75 patients with early-stage ($n = 14$; 2 stage II, 12 stage IIIA) and pretreated late-stage ($n = 61$; 15 stage IIIB, 46 stage IV) NSCLC was designed to define the dose-related effect of belagenpumatucel-L. Each patient received 1 of 3 dose levels (1.25×10^7 , 2.5×10^7 , or 5.0×10^7 cells/injection) of belagenpumatucel-L either monthly or bimonthly, for a maximum of 16 injections. The treatment was well tolerated with no severe side effects.⁵⁵ Patients with pretreated late-stage NSCLC had a 15% partial response rate. A dose-related survival difference was demonstrated in patients who received 2.5×10^7 cells/injection ($P = 0.0069$). The median OS was 14.5 months. Estimated probabilities of survival at 1 and 2 years were 68% and 52%, respectively, for the higher-dose groups combined, and 39% and 20%, respectively, for the low-dose group. Immune function was evaluated in the 61 patients with stage IIIB and IV NSCLC. Greater cytokine production at week 12, compared to patients with progressive disease, was observed among clinical responders (IFN- γ , $P = 0.006$; IL-6, $P = 0.004$; IL-4, $P = 0.007$). Furthermore, positive ELISPOT tests showed a correlation ($P = 0.086$) with clinical response in patients achieving at least stable disease. These intriguing results have prompted an ongoing phase III study of belagenpumatucel-L in patients with advanced NSCLC following front-line chemotherapy (STOP trial).

POTENTIAL ROLE FOR BIOMARKERS

With the recent clinical success of modern immunotherapeutics come new dilemmas. As noted, ipilimumab and sipuleucel-T, among other therapeutic cancer vaccines, have demonstrated an OS benefit without changes in time to progression.^{18,50} Although there may be rational immunologic and clinical explanations for this phenomenon, clinicians charged with making treatment decisions are left to wonder how to assess long- and short-term benefits.⁵⁶ There is an obvious role for standardized immune response biomarkers to help determine clinical benefit soon after immunotherapy. These readouts should determine if additional therapy is required and when it should commence. Many assays have been described in the literature, but none has found a standardized role. Some are very specific, such as the ELISPOT assay, which determines antigen-specific T-cell activation through individual cell gamma-interferon production in response to an APC expressing the specific TAA.⁵⁷ The major flaw with the ELISPOT assays is reproducibility, which may vary from reader to reader or institution to institution.^{58,59} Attempts to standardize or automate ELISPOT assays are ongoing.⁶⁰

Even if assays were standardized, allowing for more uniform readings, they would not account for antigen cascade, whereby the most relevant immune response may not be targeting the TAA specified by a given vaccine. As previously demonstrated, an antigen cascade following a vaccine-mediated immune response may result in the targeting of multiple antigens not specified by that particular vaccine.⁵ Furthermore, the most relevant TAA may vary among patients treated with the same therapeutic cancer vaccine. With agents such as ipilimumab, which allow for a more nonspecific, less targeted immune response, it is less clear which specific TAAs are most likely to be targeted. Thus, while evidence of a specific immune response against a specified TAA may support the efficacy of an immune-based treatment, the absence of that response may not preclude an immune response to a more relevant secondary antigen as an indicator of potent antitumor immune effect.

This perspective suggests the wisdom of identifying a more generalized marker of immune response. Several trials, including the IMPACT trial, evaluated T-cell proliferation in response to antigens specified in the vaccine and found that enhanced T-cell proliferation is associated with improved outcomes.¹⁸ These tests, however, lack sensitivity, and thus it remains unclear if the absence of such responses precludes benefit.

Multiple methods have been employed to evaluate cytokine production in response to immunotherapy. However, cytokine detection by ELISA assays are highly variable among different patients and the overall sensitivity of this test is low. Conversely, RT-PCR analysis, which is highly sensitive and reproducible, can evaluate cytokine production measuring mRNA. The drawback of this technique is that mRNA analysis necessitates destruction of the immune cell, which prevents determination of the T-cell specificity.⁶¹

Another general parameter of immune activation has been evaluated in trials of sipuleucel-T. A previous analysis suggested that CD54 is a marker of APC activation, and that CD54 expression after cell-product preparation could be used to assess APC engagement and vaccine efficacy.^{62,63} This strategy was evaluated in selected patients from the IMPACT trial and was again associated with improved survival outcomes.⁶⁴ Nonetheless, the ultimate clinical utility of assessing CD54 status remains unclear, and it is likely that more prospective data will be required. Furthermore, the potential role of CD54 analysis in conjunction with other immune therapies has not been thoroughly evaluated.

These and other techniques for assessing immune biomarkers need further prospective evaluation in patients treated with modern immunotherapeutics. Although it took decades

for therapeutic cancer vaccines to demonstrate clinical efficacy, their ultimate utility could be substantially limited by the lack of useful biomarkers. Clearly, this is the most pressing need for clinicians as these agents evolve from experimental to standard therapies.

CONCLUSIONS

Therapeutic cancer vaccines have been in development for several decades, initially with disappointing results. But those initial failures increased our understanding of the immune antitumor response and prompted the development of modern immunotherapeutic agents that are considerably less toxic than conventional chemotherapies and targeted molecular therapies. Recent clinical trial results with sipuleucel-T have shown that the immune response induced by a therapeutic cancer vaccine can have a significant clinical impact. Additional strategies are being investigated, many in late clinical development. Combinations of vaccines, standard therapeutics, and other immune-regulating agents are also under investigation. After years of preclinical and clinical development, medical oncologists and their patients are finally beginning to experience the potential benefits of enhanced immune responses targeting specific malignancies.

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Table 1

Possible mechanisms by which standard therapies may enhance therapeutic cancer vaccines.

Modality	Proposed mechanism of action
<i>Radiation therapy</i>	Irradiation-induced up-regulation of genes: Fas, MHC class I, and ICAM-1
<i>Chemotherapy</i>	Up-regulation of MHC class I and TAAs on the surface of tumor cells, depletion of regulatory T cells (cyclophosphamide), increase in macrophage antitumor activity and apoptosis (doxorubicin), increase in proinflammatory cytokine production (docetaxel), alteration of balance between effectors T cells and Tregs / decrease in Treg function (sunitinib, pan-BCL-2 inhibitor GX15-070)
<i>Androgen-deprivation therapy</i>	Induction of T-cell infiltration in the human prostate, enhancement of the T-cell repertoire, abrogation of immune tolerance to the prostate

ICAM-1 = intercellular adhesion molecule 1

MHC = major histocompatibility complex

TAA = tumor-associated antigen

Table 2

Therapeutic cancer vaccines discussed in this article.

Vaccine	Indication (phase)	Description	Clinical observation	Reference
<i>Sipuleucel-T (Provenge™)</i>	Metastatic prostate cancer (FDA-approved)	PAP-loaded autologous APCs	Prolonged median OS by 4.1 months compared to placebo (25.8 vs. 21.7 months) and reduced risk of death from any cause by 22.5%.	18
<i>PSA-TRICOM</i>	Metastatic prostate cancer (phase II; phase III planned)	Recombinant poxviral vaccine activates CTLs to target PSA-expressing cells	82 patients received vaccine and 40 patients received vector. Results showed improved median OS by 8.5 months (25.1 vs. 16.6 months) and stratified log-rank $P = 0.0061$.	19
<i>MAGE-A3 (GSK1572932A)</i>	MAGE-A3 positive stage IB or II NSCLC (phase III ongoing)	Patients who carry the HLA-A1 allele and express MAGE-A3 (about 35% of NSCLC patients)	182 (stage IB – II) patients were enrolled; 30.6% had recurred in the vaccine arm vs. 43.3% in the placebo arm. No statistical significance was found; however, median OS favored the vaccine group.	36
<i>L-BLP25 (Stimuvax™)</i>	Stage IIIB or IV NSCLC (phase III ongoing)	A liposome-encapsulated peptide derived from MUC1	Median OS was 17.4 months for the vaccine arm vs. 13.0 months for the placebo arm ($P = 0.112$). A subgroup analysis suggested the greatest benefit in patients with stage IIIB locoregional disease ($P = 0.069$).	29
<i>BiovaxID</i>	Non-Hodgkin's lymphoma (phase III)	An anti-idiotype patient-specific protein	At a median follow-up of 56.6 months median time to relapse for the vaccine arm was 44.2 months vs. 30.6 months for the placebo arm ($P = 0.045$).	40
<i>Ipilimumab</i>	Advanced melanoma (phase III); metastatic prostate cancer (phase II)	Human antibody that binds CTLA-4 antigen	Patients given ipilimumab plus GP100 vaccine had a median survival of 10 months vs. 6.4 months for patients given vaccine alone ($P < 0.001$). Median OS with ipilimumab alone was 10.1 months ($P = 0.003$).	51
<i>Belagenpumatucel-L (Lucanix™)</i>	NSCLC (phase III ongoing)	Allogeneic NSCLC cells transfected with a plasmid containing a TGF- β 2 antisense transgene	A dose-related survival difference was seen in patients who received a higher dose of vaccine (2.5×10^7 cells/injection, $P = 0.0069$). The estimated survival at 1 and 2 years respectively was 68% and 52% for the high-dose and 39% and 20% for the low-dose vaccine group.	55

APC = antigen-presenting cell

CTL = cytotoxic T lymphocyte

CTLA-4 = cytotoxic T lymphocyte-associated antigen 4

GP100 = glycoprotein 100 melanoma antigen

HLA = human leukocyte antigen

MAGE-A3 = melanoma antigen A3

MUC1 = mucin 1 antigen

NSCLC = non-small cell lung cancer

OS = overall survival

PAP = prostatic acid phosphatase