Cancer Vaccines: Can They Improve Survival?

Robert O. Dillman

Abstract

In patients with metastatic cancer, therapeutic anticancer vaccines are rarely associated with objective antitumor responses; so, many investigators have focused on progression-free survival (PFS) as a key endpoint for clinical trials. However, it is not clear that PFS is a surrogate for overall survival (OS), and OS may be a more appropriate endpoint because of the effects on long-term memory in the adaptive immune system. Recently, reported vaccine trials were reviewed to determine their primary and secondary endpoints and results. Randomized trials testing sipuleucel-T and prostatic acid phosphatase (PAP) in prostate cancer and ipilimumab and eltrapuldencel-T in melanoma were associated with low objective response rates, no improvement in PFS, but statistically significant improvement in OS. Although compared with PFS, it takes longer to get a final result when OS is the primary endpoint; there is increasing evidence that if long-term memory recognition of tumor-associated antigens is the mechanism of action of an investigational product, then OS may be the only valid clinical endpoint for efficacy.

Key words: cancer vaccines, melanoma, overall survival, prostate cancer

Introduction

Because of their minimal toxicity, there has been longstanding interest in the potential benefit of therapeutic vaccines in the setting of metastatic cancer, especially melanoma.¹ Unfortunately, even if a vaccine can induce or enhance a response to one or more tumor-associated antigens (TAAs), most studies have failed to document a clinical benefit.² Notable failures have included allogeneic cell lines in melanoma,³ gp100 in melanoma,⁴ and anti-idiotypic vaccines in lymphoma.⁵ However, potential vaccines vary in terms of their antigen sources, adjuvants, and routes and schedules of administration; so, one should not conclude that all therapeutic vaccines are ineffective.^{2,6} The theoretical limitations of allogeneic, single-antigen, and oligo-antigen vaccines have been noted, and there has been increasing focus on autologous TAAs.^{7,8} There is also the promising potential for combining vaccines with anticheckpoint monoclonal antibodies.⁹

However, what is the best endpoint to document clinical efficacy in trials of therapeutic vaccines and related immunotherapies? And a related question, can cancer vaccines prolong survival? In 1996, the author authored an article entitled "Why event-free survival is better than tumor response or other measures of survival as an endpoint in cancer trials."¹⁰ The term event-free survival (EFS) from that era is

synonymous with what is known today as progression-free survival (PFS), with endpoints defined by the date of death or the date of disease progression, whichever comes first. However, overall survival (OS), defined by the date of death from any cause, is usually considered the most meaningful endpoint and has continued to be the gold standard for efficacy in clinical trials.¹¹ In patients with metastatic cancer, therapeutic anticancer vaccines are rarely associated with objective antitumor responses; so, many investigators have focused on PFS as an endpoint for clinical trials. While PFS often is a surrogate for OS in cancer chemotherapy trials, it is not clear that PFS is a surrogate for OS when the mechanism of action of an immunotherapy product is long-term memory in the adaptive immune system.

Methods

Recent publications, related to four products that have been tested in prostate cancer and/or melanoma, were reviewed. Sipuleucel-T is an autologous dendritic cell (DC) product for prostate cancer that expresses a recombinant fusion protein that produces prostatic acid phosphatase (PAP) as a TAA and granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant.¹² It is administered intravenously (i.v.) every 2 weeks for three doses.

NeoStem, Inc., New York, New York.

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Address correspondence to: Robert O. Dillman; NeoStem, Inc., 18301 Von Karman Avenue, Suite 130, Irvine, CA 92612
E-mail: rdillman@neostem.inc

Prostvac-vf, previously known as prostate-specific antigen (PSA)-Tricom, is an antiprostata cancer vaccine that consists of two recombinant viral vectors encoding PSA as the TAA and three costimulatory molecules, B7.1, ICAM-1, and LFA-3.¹³ It is administered subcutaneously (s.c.) on days 1, 14, 28, 56, 84, 112, and 140, and 100 μ g GM-CSF is injected nearby as an adjuvant on the day of each injection and for the following 3 days. Eltrapuldencel-T (formerly referred to as melapuldencel-T) is a patient-specific antimelanoma vaccine consisting of autologous DCs loaded with TAAs from irradiated autologous tumor cells (TCs) derived from a short-term autologous TC line.¹⁴ It is administered on weeks 1,2,3,8,12,16,20, and 24, and each dose of cells is suspended in 500 μ g GM-CSF for each s.c. injection.

Ipilimumab is not considered a vaccine, but its primary mechanism of action is believed to be enhanced recognition of TAAs. It is a human monoclonal antibody extensively tested in metastatic melanoma that blocks the anticytotoxic T lymphocyte antigen-4 (CTLA-4) molecule that inhibits DC presentation of TAAs to host T cells that lead to memory and cytotoxic T cells.¹⁵ It is administered i.v. every 3 weeks for four doses. A recent publication showed that patients treated with ipilimumab, who experienced long-term survival, each had uniquely mutated antigens that share immunogenic tetrapeptide sequences that can elicit responses from T cells.¹⁶

Results

Sipuleucel-T

In the course of multiple trials, sipuleucel-T was associated with rare objective tumor responses in patients with prostate cancer, and there were no differences in PFS compared with control arms, but there were consistent differences in OS. In the first trial, 127 patients with asymptomatic, castrate-resistant, metastatic prostate cancer were randomized 2:1, with 82 receiving sipuleucel-T and 45 receiving placebo. This trial barely missed the primary endpoint of time to progression (median 12 vs. 10 weeks, $p=0.052$), but for the secondary endpoint, there was a difference in OS, median 26 versus 21 months ($p=0.01$).¹⁷

An identical trial was performed in an additional 98 patients who were castrate resistant. Once again, there was no difference in PFS ($p=0.72$), but there was a 21% reduction in the risk of death ($p=0.33$).¹⁸ The data from this trial were pooled with data for 127 patients from the first trial, resulting in 147 patients treated with sipuleucel-T and 78 in the control arm.¹⁸ As would be expected, there was no difference in PFS between the two arms. In this pooled data set, only 3% of patients treated with sipuleucel-T had a reduction in PSA compared with none in the control arm. However, the pooled data again showed an improved OS ($p=0.01$, HR=0.67) for patients who received sipuleucel-T. A similar trial was conducted in prostate cancer patients who were still androgen dependent.

The time to biochemical failure defined by increasing PSA was no better in 117 patients who received sipuleucel-T than 59 control patients ($p=0.74$, HR=0.94).¹⁹ Because survival is so much better in these patients who are not yet castrate resistant, OS was not an endpoint because of the minimal number of death events during follow-up. The trial that resulted in regulatory approval for commercial marketing of this product enrolled 512 castrate-resistant patients

in a 2:1 ratio with OS as the primary endpoint. The 341 patients randomized to receive sipuleucel-T had a median OS of 26 months compared with 22 months in the control arm, an 18% increase in median survival with 3-year survival rates of about 30% versus 20%, ($p=0.03$, HR=0.78), or a 50% increase the proportion surviving 3 years.²⁰ Once again, there was no difference in time to disease progression (3.7 versus 3.6 months, $p=0.63$). This product would never have been approved if the developers had not conducted additional trials that focused on OS as the primary endpoint.

Prostvac-VF (PSA-Tricom)

In a double-blind, 2:1 randomized trial, 82 patients with castration-resistant metastatic prostate cancer received the prostvac-vf vaccine plus GM-CSF and 40 received control vectors and GM-CSF. The planned primary endpoint in this trial was PFS, but the median PFS was 3.8 and 3.7 months with no difference in the curves ($p=0.60$, HR=0.88).²¹ However, there was a substantial difference in OS, although the curves did not separate until after 1 year of follow-up. With a minimum follow-up of 3 years, the median OS was 25 versus 17 months, respectively ($p=0.01$, and HR=0.58), that is, a 47% increase in median survival.

In another study, National Cancer Institute investigators examined serum PSA levels to determine growth rate kinetics for 268 prostate cancer patients enrolled in five intramural trials, including 47 patients treated with PSA-tricom.^{6,22} Even though there was no evidence of tumor regression, follow-up revealed that patients treated with the vaccine had a better long-term survival than those treated with chemotherapy, consistent with an ongoing immune response. Furthermore, the slowing of tumor growth rate correlated with OS and was a better predictor of outcome than PSA-doubling time.

Eltrapuldencel-T

In 74 patients who had experienced metastatic melanoma, injections of irradiated autologous TCs as the source of TAAs, were associated with an ORR of less than 10% among 35 patients with measurable or evaluable disease. The EFS was only 4.4 months, 3-year EFS 21%, and 5-year EFS 19%, but median OS was 20.5 months, 3-year OS 36%, and actual 5-year OS 28%.²³ The low ORR was typical of many treatments in melanoma, but with less toxicity, and the PFS was similar to what was reported in contemporary trials with intravenous interleukin-2.^{24,25} The 5-year survival rate of 28% seemed surprisingly good given a 5-year survival rate of only about 10% for such patients nationally.²⁶ Was this a biased patient population based on unintentional selection issues, or was this a long-term benefit from the vaccine?

A subsequent trial used the same autologous cell sources for TAAs, but relied on DCs to present the TAA after cocubation with irradiated TCs to produce a product referred to as DC-TC. In this trial, DCs were loaded with tumor antigens *ex vivo*, and then injected into the patient, as opposed to direct injection of TCs as the source of TAAs. In patients who had experienced metastatic melanoma, the ORR was 0/15 for patients with measurable disease, and the median EFS was 4.2 months and 5-year PFS 23% for all 54 patients,²⁷ which was similar to the observations in the 74-

patient TC trial. However, once again survival was surprisingly good, with an actual 5-year OS (all patients followed to death or minimum of 5 years and no patients lost to follow-up) of 50% (54% projected at the time of publication). Was this an even more favorable patient population, or was this a better survival benefit because of the TAA presentation by *ex vivo* loaded DCs (DC-TC)? Only a randomized trial could provide an answer to this question.

Based on the consistency of the observations across these two trials, which were conducted with similar eligibility criteria and treatment schedule, it was concluded that OS was a more important endpoint than ORR or PFS. The results were also consistent with the concept of targeting tumor stem cells.²⁸

Since true benefit could not be established in an open-label single-arm study, a randomized trial was conducted using the same eligibility criteria as the previous trials, with DC-TC in one arm and TCs in the other, and both products suspended in GM-CSF. For this trial, OS was the primary endpoint. When this trial was stopped early, the median OS was 32 months and 5-year survival 38% at a time when 21/42 patients had died with minimum follow-up of 2.5 years and no patients lost to follow-up.²⁹ The DC-TC arm was associated with a longer survival with a median OS of 43 versus 20 months (a 115% increase in median survival) and a doubling of the 2-year OS at 72% vs. 31% ($p=0.007$). There were no measurable responses in either arm of the trial, although one patient in the DC-TC arm, who had new, progressing measurable disease, had stabilization during treatment that evolved to a complete response by 15 months after initiation of the vaccine, in the absence of any other therapy,³⁰ and was still in remission 5 years after initiating DC-TC therapy. The median EFS in this trial was 5.3 months overall, 5.4 months for DC-TC, and 3.7 months for TCs ($p=0.44$).

Ipilimumab

In animal models, the combination of anti-CTLA4 antibody and peptide vaccine was better than either agent alone.³¹ For this reason, much of its development was in conjunction with a peptide vaccine targeting the gp100 (HMB45) differentiation antigen. The pivotal trial was limited to patients who were HLA-2 positive with 676 randomized 3:1:1 to ipilimumab + gp100, ipilimumab alone, or gp100 alone.⁴ In hindsight, perhaps it is not surprising that vaccination against a single common TAA failed to add any clinical benefit to ipilimumab, especially when it is known that endogenous DCs presumably are trying to present numerous TAAs to T cells all of the time in patients with advanced cancer. For this product, one might predict it would take time to generate an immune response to exposed TAAs, and if these TAAs are not ubiquitous on differentiated TCs in tumor masses, one would not expect a great effect in terms of ORR or PFS. At this time, it is not known how many of the patients had underlying immune recognition of gp100 that was being suppressed by CTLA4.

In the pivotal trial, the ORR was only 6% for the 540 patients who received ipilimumab compared with 2% for gp100 alone.⁴ However, it was well documented that several patients had disease stabilization or even disease progression that was followed by subsequent regression. More importantly, a long-term survival benefit was observed for the entire cohort of patients treated with ipilimumab. In-

vestigators and the sponsor recognized this and changed the primary endpoint of this trial from PFS to OS. At the final analysis, the median PFS was 2.8–2.9 months in all three arms, but there was a marked difference in OS with a median of 10 months for the ipilimumab-treated patients compared with only 6 months for the cohort that received gp100 alone ($p<0.001$, HR=0.66), a 67% increase in the median survival.⁴ Long-term follow-up has confirmed 4-year OS rates of about 20%.³² GM-CSF was not a component of this trial, but recently a randomized trial found an advantage for GM-CSF plus ipilimumab compared with ipilimumab alone, with 1-year survival rates of 69% versus 53% ($p=0.01$, one-sided).³³

Recently, additional monoclonal antibody checkpoint inhibitors that target programmed death molecules (PD-1, PDL-1) have been approved for the treatment of metastatic melanoma.^{34–36} Unlike ipilimumab, nivolumab and pembrolizumab were initially approved based on high objective response rates. However, it is also evident that tumor regression is delayed in many patients treated with these products, and long-term survival is more impressive than the actual response rates or PFS.^{37,38}

Discussion

The results of trials with the above products suggest that enhancing recognition of TAAs can be associated with improved OS, despite rare objective responses and no improvement in PFS. Given the perceived mechanism of action for these vaccine products, this lack of correlation between ORR, PFS, and OS should not be surprising. In each case, immune recognition of TAAs has to be induced, or enhanced, which takes time. Furthermore, in some, if not all instances, it may only be a subset of cells that express the most relevant TAAs. For instance, in the case of eltrapuldencel-T, the source of TAAs is self-renewing proliferating cells that share many characteristics with tumor stem cells.⁷ If such early tumor-initiating cells are being targeted preferentially, and many of their TAAs are not expressed on more differentiated TCs, then one would not expect any immediate effects on existing tumor lesions, including those that are not detectable, and these sites might increase after a few more proliferations of soon-to-be terminally differentiated TCs. However, if one is inducing or stimulating long-term memory T cells and an effective cellular and humoral response against TAAs on a subset of tumor stem cells and/or early progenitors, then one might get a long-term survival benefit without any suggestion of benefit based on ORR or PFS.

So, what about the specific immune responses that are being induced? It is known from numerous reports with various peptide vaccines that specific immune responses can be induced or enhanced in cancer patients by vaccination. Autologous vaccine products present a challenge in terms of measurement of immune response because of TAA heterogeneity among patients. Although there may be some common expression of certain TAAs, it is now known that every patient harbors unique neoantigens that result from their mutations. Tumors from melanoma patients express tens to hundreds of thousands of mutated proteins, many of which are nonsynonymous and therefore potentially antigenic.^{39,40} In elegant work from the United States National Cancer Institute (NCI), complete exomic analyses and tumor-infiltrating lymphocytes have been used to prove that such unique

antigens can be targeted by the patient's immune system and induce durable responses when billions of cells are infused after ablation of the host immune cells.^{41,42} Recently, similar exomic and neoepitope analyses were used to show that the patients who derive long-term survival benefit from ipilimumab are also recognizing epitopes on uniquely mutated antigens.¹⁶

It should be noted that once upon a time PFS actually meant what it said, that is, it was defined only by the date of disease progression, and if patients died of another cause, they were censored from survival analysis as of that date. However, some trials, especially bone marrow transplant trials, came under attack for focusing on PFS rather than OS because so many patients were dying from the toxicity of therapy and being excluded in PFS analyses. Somewhere along the line, thought leaders and regulatory authorities decided to change the definition of PFS to include death,⁴³ thereby making it synonymous with the former EFS definition. If one is comparing clinical trials over time, it is important to be sure what is meant by PFS in any specific publication because, in older trials, it meant time to disease progression, whereas in the past decade, it increasingly has meant death or progressive disease.

In the 1996 article cited earlier,¹⁰ many of the problems associated with ORR were enumerated, most of which persist today, and an argument was made for the increased use of EFS (PFS today) rather than ORR or OS as the key endpoint, not only for phase III trials but also in phase II trials involving biologics. The use of OS as the key endpoint was considered less desirable because of the length of time needed in follow-up before appropriate statistical analysis could be performed, and because increased numbers of treatment options could confound cause and effect for any specific therapy or combinations of therapies. When that article was written, the focus was on the challenges of assessing emerging therapeutic vaccines by other than the traditional chemotherapy models. It was noted that this might be especially important for biological therapies, including immunotherapies, and a specific example was provided, namely the analysis of metastatic melanoma patients rendered free of disease by surgery. The evidence cited in the current article suggests that OS is a better endpoint than PFS for evaluation of such vaccines.

Although ORR and PFS are often considered as surrogates for OS, whether they can serve as surrogates for OS depends on the specific cancer type, the specific agents being tested, and the absence of other effective therapies. However, PFS has become very popular because when disease progression is the endpoint, a trial can be concluded much faster than if OS is the endpoint. Pitfalls associated with the use of PFS as an endpoint have been pointed out in other publications.^{43,44} The same issues that confound PFS also confound ORR. Measurement of tumor size is imprecise; so, definition of time of date of disease progression and ORR are imprecise, and thresholds for defining progression are arbitrary. Second, if one wishes to use PFS as the endpoint, then it is essential that repeated measurements of the tumor be performed at frequent prescribed intervals to avoid various bias pitfalls that affect the timing of declaration of disease progression. This results in excessive testing that is costly and is associated with increased radiation exposure. Third, contrary to the original hypothesis for why PFS

would be better than OS for immunotherapies, it turns out that ORR and PFS are not reliable surrogate endpoints for many emerging cancer immunotherapies because of their mechanism of action, and yet these agents are associated with improved long-term OS. Given the current understanding of the immune system and tumor immunology and memory in the adaptive immune system, for certain products, OS may be the only relevant efficacy endpoint and therefore remains the gold standard.

Disclosure Statement

No competing financial interests exist.

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