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Therapeutic cancer vaccine fulfills the promise of immunotherapy in prostate cancer

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Abstract

For many years, preclinical and clinical studies have attempted to harness the power of the immune system and focus it on malignant cells in an attempt to improve clinical outcomes for patients with cancer. The current paper describes the landmark phase III trial that led to the first U.S. Food and Drug Administration approval of a therapeutic cancer vaccine. In a randomized trial of 512 patients, those treated with sipuleucel-T survived for 25.8 months compared to those treated with placebo, who survived 21.7 months (hazard ratio 0.78; p = 0.03). There was, however, no change in time to progression, which may speak to the underlying mechanism of this new class of therapeutics.

Keywords

metastatic prostate cancer; therapeutic cancer vaccines; overall survival; immunotherapy; minimal toxicity

For patients with metastatic castration-resistant prostate cancer (mCRPC), testosterone-lowering agents no longer effectively control the spread of disease. Second-line hormonal therapies that target the androgen receptor (androgen receptor antagonists) or secondary sources of testosterone production (ketoconazole) are commonly employed for patients with symptomatic mCRPC in an effort to delay progression [1]. For patients with symptomatic disease, chemotherapy is commonly used. It was not until 2004 that the chemotherapy regimen of docetaxel with prednisone first demonstrated an improvement in overall survival of approximately 3 months relative to mitoxantrone and prednisone, the previous regimen approved by the U.S. Food and Drug Administration (FDA) for palliation [2–4]. It would take 6 years before another chemotherapy regimen (carbazitaxel and prednisone) demonstrated a survival benefit in patients who progressed on docetaxel [5].

In spite of these successes, numerous clinical trials with a broad range of therapeutics in mCRPC have failed to demonstrate significant changes in overall survival, and mCRPC treatments have remained an active field of research. Among the treatments studied for patients with mCRPC are therapeutic cancer vaccines. The relatively indolent nature of prostate cancer, compared to other types of metastatic disease, allows time for an immune response to be generated, making it a good candidate for immune-based therapies. There are also many unique tumor-associated antigens (TAAs) expressed on normal prostate and

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prostate cancer cells, allowing for effective targeting of immunologic agents. Among these TAAs are prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) [6–9].

Sipuleucel-T is a patient-specific therapeutic cancer vaccine, derived from the patient's own immune cells, that targets PAP. Peripheral blood mononuclear cells are collected via leukapheresis and stimulated *ex vivo* by a PAP/GM-CSF fusion protein (PA2024). The resulting patient-specific, activated cellular product is then re-infused into the patient. A full course of treatment in the phase III trial entails repeating this entire process every 2 weeks for a total of 3 doses [10, 11]. Early clinical trials demonstrated this agent's safety and ability to generate an immune response [12, 13]. Subsequently, 2 small phase III trials were conducted in mCRPC, with time to progression (TTP) as the primary endpoint. When the first of these 2 trials failed to meet this endpoint, the second trial was closed prematurely. An ensuing analysis of the data from these trials, however, demonstrated an overall survival benefit in patients treated with sipuleucel-T [14, 15]. The FDA suggested that the company complete its then ongoing overall survival endpoint study to confirm these findings. The trial presented in this paper is the follow-up definitive trial of sipuleucel-T in mCRPC, and this time overall survival was the primary endpoint.

Summary of methods & results

The study enrolled 512 patients at 75 centers in the United States and Canada. Patients were required to have progressive mCRPC as determined by either rising PSA or new or enlarging lesions on imaging studies. Other eligibility criteria included PSA > 5 ng/mL and testosterone < 50 ng/dL. Initially, a Gleason of ≤7 was required, but the protocol was later amended to enroll patients regardless of Gleason score, based on survival data from the previous studies. Patients were excluded if they had an Eastern Cooperative Oncology Group performance status of ≥ 2, a history of pathological fractures of long bones, visceral metastasis, or spinal cord compression. Previous therapies were limited to 2 prior chemotherapy regimens, none in the 3 months prior to enrollment.

Patients were randomized 2:1 in favor of treatment with sipuleucel-T and were stratified by primary Gleason score, number of bone metastases, and use of concomitant bisphosphonate therapy. Sipuleucel-T or placebo was infused every 2 weeks for a total of 3 infusions. Patients were monitored with computed tomography at weeks 6, 14, 26, 34, and every 12 weeks thereafter, and bone scans at weeks 6, 10, 14,18, 22, 26, 34, and every 12 weeks thereafter. Immune monitoring was performed in a subgroup of patients at weeks 6, 14, and 26. Progression was determined based on central scan review.

Patients in the placebo arm were allowed to be unblinded at progression and treated with a salvage agent (APC8015F) at the discretion of their treating physician. The agent consisted of cells prepared in the same manner as sipuleucel-T at the time of placebo production, then cryopreserved.

The primary endpoint of the study was overall survival, with TTP as a secondary endpoint. The study was designed to enroll a minimum of 500 patients, with a power of 88% to detect a 31% risk reduction in death on the sipuleucel-T arm, with a 2-tailed alpha of 0.05. The median overall survival was 25.8 months in the sipuleucel-T arm, compared to 21.7 months in the placebo arm. At 3 years, 31.7% of patients in the sipuleucel-T arm were alive, compared to 23.0% in the placebo arm. This translated into a reduction in risk of death in the sipuleucel-T arm of 22% ($p = 0.02$); the adjusted hazard ratio for death was 0.78 with a 95% confidence interval of 0.61–0.98. The time to objective median progression was 3.7 months in the sipuleucel-T arm, compared to 3.6 months in the placebo arm ($p = 0.63$). Among patients treated with sipuleucel-T, < 3% had PSA declines and only 1 had an objective partial response. Adverse events associated with sipuleucel-T consisted primarily of

transient chills, fever, and nausea. It should be noted that the adverse event profile for sipuleucel-T has a minimal impact on quality of life, relative to the cytotoxic side effects of chemotherapy.

Analysis of immune responses included evaluation of antibody response and T-cell proliferation assays in a subset of patients. Based on the relatively cursory immune analysis, there remain no clear immunologic markers of efficacy.

Discussion & significance

Patients in each arm of the trial appeared to be well balanced in terms of baseline characteristics and treatment histories. Although the sipuleucel-T arm included more patients with metastasis only to bone (50.7% vs. 43.3%), no data suggest that this had any prognostic implications [16]. Kantoff *et al.* present a detailed analysis of the effects of subsequent chemotherapy on patients in both arms of the study (57.2% from the sipuleucel-T arm; 50.3% from the placebo arm). The data suggest that subsequent docetaxel chemotherapy did not significantly influence survival outcomes for either treatment arm, and cannot account for the improvement in overall survival seen in the sipuleucel-T arm. Incidentally, it is not surprising that so few patients received docetaxel, as men with mCRPC are often reluctant to receive chemotherapy, preferring to enroll in immunotherapy trials. Similar proportions of patients have declined future chemotherapy in trials of other prostate cancer vaccines [17, 18].

A review of the study's design demonstrates a unique characteristic for a trial with overall survival as an endpoint. Patients on the placebo arm had the option (at the discretion of the treating physician) to receive a cryopreserved form of sipuleucel-T produced at the time of enrollment. This is a confounding variable that some have suggested delayed the administration of effective chemotherapy for patients in the placebo arm, potentially affecting their survival. However, the delay in chemotherapy administration was minimal (median 12.3 months in the sipuleucel-T arm vs. 13.9 months in the placebo arm). Given that the median time until chemotherapy for both groups was more than a year, it is unlikely that an additional month of therapy for those receiving the cryopreserved agent meaningfully delayed chemotherapy for the majority of patients. In addition, there are no data to suggest that patients with mCRPC who receive chemotherapy earlier have better outcomes. Ultimately, the overall survival of patients in the placebo arm (21.7 months) is comparable to the median survival of patients in a contemporary phase III trial who received a standard regimen of docetaxel (21.5 months) [19].

The outcome of this study is significant because it led to the first FDA approval of a therapeutic cancer vaccine, one of only 3 approved therapies by the FDA for patients with mCRPC. It will give patients with minimal symptoms a treatment option other than standard chemotherapy and second-line hormonal agents. In addition, The side effect profile for this agent is much more favorable than that of chemotherapy. The results of this study will likely give added momentum to efforts to develop therapeutic cancer vaccines for this and other cancers.

This study may also provide insight into the unique characteristics of novel immune therapeutics, such as the phenomenon of improved survival without change in TTP. Emerging data suggest that this outcome may be a class effect. This possibility is supported by recent clinical data on PSA-TRICOM, another prostate cancer vaccine, and an anti-CTLA-4 monoclonal antibody used to treat patients with metastatic melanoma. PSA-TRICOM is a vector-based vaccine that targets PSA in patients with prostate cancer. A recent multicenter study randomized 125 patients 2:1 in favor of the vaccine. Although there was no change in TTP, there was a > 8-month improvement in overall survival ($p = 0.0061$)

[20]. Similar results were seen with ipilimumab, which blocks the immune-regulating CTLA-4 molecule on T cells, thereby enhancing T cell-mediated immune responses. In a recent phase III study, patients were randomized to active control (GP100), ipilimumab, or ipilimumab and GP100. Although median TTP was 2.8–2.9 months in all 3 arms, ipilimumab-treated patients lived approximately 4 months longer ($p \leq 0.003$) than patients treated with active control alone [21].

There are several possible explanations for these findings. First, unlike cytotoxic agents, no immediate reduction in tumor volume is expected. It likely takes time to generate an effective immune response, and during this time, the tumor growth rate may remain unchanged. This could be interpreted as disease progression by conventional measures such as RECIST, which measure response by changes on imaging alone. It is also possible that the active immune response generated by these modern immunotherapies potentiates an antitumor response that persists after the immune treatment is discontinued [22]. Subsequent therapies that kill tumor cells in the presence of an active immune response may serve as a vaccine “booster” by exposing the immune system to additional antigens to target, potentially broadening and enhancing the immune response [23–27]. Subsequent radiation or chemotherapy can also phenotypically alter tumor cells, making them more susceptible to immune-mediated killing [27–30]. In addition, standard antitumor agents have been shown to trigger molecular “signaling,” leading to immune activation that could combine with an ongoing immune response [31, 32].

Future perspective

The approval of a first-in-class agent is always an important step forward, but the steps that follow may have the greatest impact. Given the likelihood that time is required to generate an immune response, and that subsequent therapies may enhance that immune response, a logical move would be to administer cancer vaccines into earlier stages of disease, including non-metastatic patients or into the [neo]adjuvant setting. Combination therapies of vaccine plus standard anticancer agents may also lead to improved outcomes compared to standard treatments alone. Clinical trials investigating these approaches in prostate cancer and other malignancies are ongoing.

Ultimately, however, questions remain about improved survival without changes in TTP with the use of sipuleucel-T. The lack of an intermediate endpoint such as TTP or a biomarker predictive of response complicates the issue for medical oncologists. Although immunologic data was presented, the analysis was quite limited and these parameters should not be considered surrogate markers for response. Clearly, this area of research is critical and may help determine the ultimate role of cancer vaccines in medical oncology. Perhaps an intermediate marker of response may emerge as more patients are treated with cancer vaccines. Until then, medical oncologists are advised to use sipuleucel-T in patients with minimal and indolent mCRPC and monitor them clinically for objective signs of progression beyond PSA alone.

It remains to be seen how sipuleucel-T, a radically different approach in medical oncology, will be embraced in the community setting, given its cost and complexity of production. Nonetheless, its importance as the first FDA-approved cancer vaccine cannot be overstated. Furthermore, for patients with indolent, minimally symptomatic mCRPC, sipuleucel-T represents a viable treatment option with far less toxicity than conventional chemotherapy.

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Executive summary

- Sipuleucel-T is a patient-specific therapeutic cancer vaccine, generated from a patient's own peripheral immune cells, targeting prostatic acid phosphatase.
- This randomized, phase III trial of men with metastatic castration-resistant prostate cancer demonstrated a median 4.1-month improvement in overall survival, leading to approval by the U.S. Food and Drug Administration.
- Areas of active or planned research include using therapeutic vaccines alone earlier in the disease course, combining vaccines with conventional anticancer therapies, and identifying biomarkers that can be used as intermediate markers of clinical benefit.