The evolving role of immunotherapy in prostate cancer

W. R. Gerritsen*

Department of Medical Oncology, VUmc Cancer Center Amsterdam, 1081 HV Amsterdam, The Netherlands

The prognosis for men with metastatic, castration-resistant prostate cancer (CRPC) is limited, and patients have very few treatment options, particularly if the treatment failed with docetaxel (Taxotere). As a result, there is a requirement for novel approaches to therapy. Using immunotherapy to induce immune responses to prostate cancer in preclinical and clinical studies appears to be a valid therapeutic approach. In a pivotal phase III trial, treatment with sipuleucel-T, an autologous cellular vaccine consisting of activated antigen-presenting cells loaded with prostatic acid phosphatase (PAP), gave a median overall survival of 25.8 months compared with 21.7 months for placebo-treated patients, resulting in a 22% relative reduction in the risk of death. Based on these results, sipuleucel-T became the first therapeutic vaccine approved for any type of cancer in the USA. PROSTVAC®-VF, a poxvirus-based vaccine engineered to present prostate-specific antigen (PSA) and three immune costimulatory molecules, and GVAX, a vaccine consisting of two prostate cancer cell lines (LnCAP and PC3) and genetically modified to secrete granulocyte–macrophage colony-stimulating factor (GM-CSF), both showed promising results in phase II studies, although GVAX failed to meet its primary end point of overall survival when compared with docetaxel in a phase III study. T-cell modulation is another potential immunotherapeutic strategy for CRPC. Ipilimumab, an antibody against the cytotoxic T-lymphocyte-associated antigen-4, is being evaluated in phase II/III studies, both alone and in combination with chemotherapy, radiotherapy or GVAX, with activity in prostate cancer. CRPC is one of the few tumour types where immunotherapy is the current standard of care. Further research, however, will be necessary to improve antitumour responses and clinical benefits, including the use of novel combinatorial approaches.

**Key words:** castration-resistant prostate cancer, GVAX, immunotherapy, sipuleucel-T, T-cell modulation, vaccines

**Introduction**

Prostate cancer is the second most frequently diagnosed cancer in men, accounting for ~14% of all male cancers worldwide [1]. Prostate cancer is often considered a disease of ageing; in the USA, for example, the median age at diagnosis is 67 years, with very few cases diagnosed in men <50 years [2]. Importantly, by 2050, it is estimated that approximately one-fifth of the global population will be aged ≥60 years [3], which will have profound social and economic effects and highlights the need for effective treatments in this age-related disease.

Early-stage prostate cancer is generally diagnosed by microscopic evaluation of tissue biopsies collected as a result of changes in the level of prostate-specific antigen (PSA). At this stage, surgical treatment or radiotherapy results in up to 80% of men living free from metastatic disease for 15 years [4]. Late-stage prostate cancer is initially treated by reducing tumour burden and/or the level of testosterone through radiotherapy, surgery and/or androgen deprivation using either surgical or chemical castration [5, 6]. These treatments can be effective in delaying progression so many patients die with prostate cancer rather than because of it. Eventually, however, a lot of men develop metastatic disease despite androgen ablation, and this state is referred to as castration-resistant prostate cancer (CRPC) [4].

Patients with metastatic CRPC have limited treatment options and a grim prognosis [4]. Guidelines recommend that patients with symptomatic, metastatic CRPC receive systemic chemotherapy, second-line hormonal therapy, bisphosphonates or radioisotope therapy [5, 6]. Treatment with docetaxel-based chemotherapy regimens was shown to confer a survival benefit in two phase III trials [7–9], and as a result, is the preferred first-line chemotherapy option. Nevertheless, one of the most challenging problems in the management of prostate cancer is the treatment of patients with CRPC who have failed chemotherapy with docetaxel. For these patients, two new treatment options have been registered (abiraterone and cabazitaxel). However, there has been much research into novel therapies for this subset of patients with the aim of both prolonging survival and maintaining the quality of life.

Among the many concepts under investigation, augmenting immune responses to prostate cancer has been proposed as a valid therapeutic approach, and there are a number of lines of evidence to support this. For example, studies of prostate cancer samples show evidence of intratumoural infiltration by multiple leucocyte subtypes, including natural killer cells and T cells. These data suggest that both the innate and adaptive branches of the immune system are involved in spontaneous immune responses to CRPC [10].
Many different immunotherapeutic strategies are being investigated in clinical trials of patients with CRPC, including vaccines and agents that modulate T-cell activity, both as single agents and in combination with chemotherapy, androgen ablation or radiotherapy. The aim of this review is to discuss early-phase clinical data with immunotherapies in prostate cancer and to consider how immunotherapies might be optimised for use in later-phase clinical trials.

**vaccines**

Cancer vaccines represent an evolving type of immunotherapy that can be used to present single or multiple tumour antigens to the immune system, via a variety of delivery systems, in order to prime/boost an immune response [11]. Over the last two decades, anticancer vaccines have generally yielded disappointing clinical results [12]; however, increased understanding of the immune system, tumour immunology and vaccine technologies have allowed for the development of novel vaccine approaches that may be more efficacious. Against this background, sipuleucel-T became the first therapeutic cancer vaccine to receive Food and Drug Administration approval in the USA based on the prolongation of overall survival (OS) among men with metastatic CRPC, and the results from clinical trials with PROSTVAC®-VF, a poxvirus-based vaccine, have also been encouraging, thus providing proof-of-principle for vaccines as a therapeutic approach [13–15].

**sipuleucel-t**

Treatment with sipuleucel-T comprises a number of stages (Figure 1). Autologous cells, obtained by leukapheresis, are sent to a central facility for processing, whereby they are cultured *in vitro* with a proprietary protein cassette (PA2024) that couples the vaccine target (prostatic acid phosphatase; PAP) to the granulocyte–macrophage colony-stimulating factor (GM-CSF). The activated cellular product is then shipped to the administering physician for intravenous (IV) infusion. Treatment is repeated three times over 4–6 weeks [4, 16, 17]. It is thought that the infused cells present the PAP antigen to host T cells, resulting in the T-cell activation and proliferation [17].

In the phase III IMPACT (IMmunotherapy Prostate AdenoCarcinoma Treatment) trial of 512 patients with asymptomatic or minimally symptomatic metastatic CRPC, which served as the basis for the licensing approval of sipuleucel-T, treatment with the vaccine resulted in a 4.1 month improvement in median OS compared with placebo (25.8 months versus 21.7 months, respectively) with a 22% relative reduction in the risk of death [hazard ratio (HR): 0.78, \( P = 0.03 \)] (Figure 2) [14]. Interestingly, there was a delayed onset of response, reflected in the late separation of survival curves. Despite the substantial difference in OS, sipuleucel-T did not alter progression in the short term, with no substantial difference in time to objective disease progression [18]. Delayed separation of survival curves has been reported in many clinical trials of immunotherapeutic agents and is known

![Figure 1. The predicted mechanism of action and stages of sipuleucel-T treatment for patients with castration-resistant prostate cancer (CRPC). Adapted, in part, by permission from Macmillan Publishers Ltd: Nature Biotechnology [38], copyright 2010. APC, antigen-presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IV, intravenous; PAP, prostatic acid phosphatase.](image-url)
to impact on clinical dynamics, highlighting the need for appropriate clinical end points to assess efficacy [14, 19, 20]. In the IMPACT study, sipuleucel-T was generally well tolerated, with almost all patients receiving all three infusions. Adverse events (AEs) reported more commonly by patients in the sipuleucel-T group than in the placebo group included chills, fever, headache, influenza-like illness, myalgia, hypertension, hyperhidrosis and groin pain, most of which occurred within 1 day after infusion and resolved within 1–2 days. Grade 3/4 AEs reported 1 day after infusion were uncommon, being reported in 23 of 338 patients (6.8%) in the sipuleucel-T group and 3 of 168 patients (1.8%) in the placebo group [14].

**pox-virus vaccines**

Viral vectors are attractive for immunotherapy because they mimic natural infection and can induce potent immune responses. A large number of tumour antigens and immunomodulatory genes are available for insertion into viral vectors; however, the clinical development of PSA poxviral vaccines has received most interest as a model vaccine approach [21]. PROSTVAC®-VF, for example, is a poxvirus-based vaccine engineered to contain PSA and three immune costimulatory molecules (TRICOM: B7.1, ICAM-1 and LFA-3) within a vaccinia or fowlpox virus vector. Vaccination is often enhanced by the subcutaneous coadministration of GM-CSF, which acts to further boost immune function [22].

PROSTVAC®-VF has been investigated in several phase II trials in patients with advanced prostate cancer. In a randomised phase II study of 125 patients with minimally symptomatic, metastatic CRPC, the primary end point of progression-free survival was similar between 82 patients treated with PROSTVAC®-VF and 40 patients who received empty control vectors. However, with 3 years of follow-up, patients receiving PROSTVAC®-VF had an 8.5 month improvement in median OS (25.1 months compared with 16.6 months, respectively) and a 44% reduction in the risk of death (estimated HR: 0.56; P = 0.0061) (Figure 3) [15]. Unlike the substantial toxic effect commonly observed with conventional chemotherapy, poxvirus vaccination therapy was well tolerated.

Most AEs were injection site reactions, with only a few patients experiencing associated systemic AEs such as fatigue, fever and nausea [15, 16]. In another smaller phase II study, among 32 patients vaccinated with recombinant vaccinia containing the transgenes for PSA and TRICOM, 12 patients (37.5%) had declines in serum PSA, two of whom also had decreases in index lesions. The median OS was 26.6 months and there was a trend towards improved survival for patients with greater PSA-specific T-cell responses (P = 0.055). In addition, the suppressive action of T regulatory (Treg) cells was shown to decrease following vaccination in patients surviving longer than predicted and increase in patients surviving for a shorter time than predicted [23, 24]. These data suggest PSA-specific T-cell responses and Treg functionality may have utility as prognostic markers of efficacy in future clinical trials.

Based on the encouraging results from phase II studies, patients with asymptomatic or minimally symptomatic, chemotherapy-naïve, metastatic CRPC are currently being recruited to a placebo-controlled phase III trial of PROSTVAC®-VF, with or without GM-CSF (NCT01322490).

**T-cell-modulating agents**

T-cell modulation is another promising immunotherapeutic strategy being investigated in patients with CRPC, with treatments designed to target the processes involved in T-cell survival, activation, proliferation, migration and tumour destruction providing many opportunities for therapeutic intervention.

**Ipilimumab**

Perhaps the most extensively studied method of T-cell modulation is the blockade of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), a key inhibitory molecule that downregulates the pathways of T-cell activation. Ipilimumab is
a fully human monoclonal antibody against CTLA-4 that blocks the negative regulatory signal, thereby potentiating T-cell activation, proliferation and infiltration into tumours, which may lead to tumour cell death [25].

Ipilimumab has been investigated as a monotherapy and in combination with either chemotherapy or radiotherapy in early-phase clinical studies of patients with metastatic CRPC. In a pilot trial, among 14 patients treated with a single dose of ipilimumab (3 mg/kg), 2 patients had a decline in PSA of >50%, which lasted 135 and 60 days, respectively, and 8 patients had a decline in PSA that was <50% [26]. In phase II studies, a decline in PSA of >50% was observed in 6/43 (14%) chemotherapy-naive patients who received treatment with ipilimumab (3 mg/kg) with or without a single dose of chemotherapy (docetaxel), and among 50 patients who received ipilimumab (10 mg/kg) with or without prior priming by single-fraction radiotherapy, 10 patients (20%) had confirmed PSA declines of >50%. All 10 patients had stable disease according to response evaluation criteria in solid tumours (RECIST), with the exception of 1 patient receiving ipilimumab alone, who reported a complete response for both PSA and RECIST [27, 28]. In both the studies, treatment was generally well tolerated. Mechanism-based, immune-related AEs (irAEs) were reported in patients treated with ipilimumab alone or in combination with chemotherapy or radiotherapy, and in most cases, could be managed using established treatment algorithms [27–29].

Interestingly, these phase II studies of ipilimumab reported various patterns of PSA response, with declines observed at treatment onset, after a short period of stable disease, or after an initial rise in PSA levels (within 6 months). Some late PSA responses, occurring after 6 months of treatment, were also observed [27, 28]. In clinical trials of patients with melanoma, treatment with ipilimumab monotherapy typically results in four distinct response patterns, comprising shrinkage in baseline lesions without new lesions, durable stable disease, response after an increase in total tumour burden and response in the presence of new lesions. These unique patterns of response led to the proposal of novel immune-related response criteria [20]. It is plausible, therefore, that novel response criteria may be applicable across multiple tumour types.

Based on the promising results from early-phase clinical trials, ipilimumab 10 mg/kg is currently being evaluated in two phase III clinical trials; one versus placebo in chemotherapy-naive patients with CRPC (NCT01057810) [30], and the second in patients with CRPC following treatment with chemotherapy and a single dose of bone-directed radiotherapy (NCT00861614) [31].

**Combining immunotherapeutic approaches**

One approach for the future is to explore potential synergistic activity of T-cell-modulating agents, such as ipilimumab, in combination with cancer vaccines. Early preclinical studies, for example, demonstrated that anti-CTLA-4 activity could be enhanced when combined with tumour cell-based vaccines genetically modified to secrete GM-CSF, such as GVAX [32, 33]. In a poorly immunogenic melanoma mouse model, the combination of ipilimumab with GVAX resulted in the eradication of established melanomas, while each treatment alone had little or no effect [34].

Prostate GVAX consists of two prostate cancer cell lines, LNCaP and PC3, transfected with a GM-CSF gene. Although two phase III studies of single-agent prostate GVAX in patients with CRPC were terminated early [32], the agent is currently being investigated in various combinations in different indications.

A phase I dose-escalation trial of biweekly intradermal GVAX injections and monthly ipilimumab included 12 patients in a dose-escalation cohort (0.3–5 mg/kg ipilimumab) and a subsequent 16 patients in an expansion cohort, treated with a dose of 3 mg/kg ipilimumab [35, 36]. Among all 28 patients, seven patients (25%) who had received ipilimumab (3 or 5 mg/kg) had a ≥50% decline in PSA from baseline. Of the 22 patients treated with either 3 or 5 mg/kg ipilimumab, five (23%) had confirmed partial PSA responses with a median duration of 12 months (range 2–21 months) [36]. A strong association between the PSA response and irAEs was noted; all patients in the dose-escalation cohort who had an irAE, including grade 2/3 hypophysitis and grade 3 alveolitis, also had a PSA response. Seven patients enrolled in the escalation phase and eight patients in the expansion cohort had at least stable disease on bone scans and two patients in the escalation phase had clear regression of metastases [36]. Using the Halabi nomogram, a prognostic tool derived from an analysis of patients with metastatic CRPC in cancer and leukemia group B trials that uses seven prognostic factors to project the OS of patients [37], the median predicted survival was 19 months. By comparison, the actual median OS, as of November 2011, was 29.2 months (95% CI 9.6–48.8) [35, 36].

Additionally, data from a serological analysis suggested that patients with increased reactivity against the prostate-specific membrane antigen (PSMA) had significantly increased survival. Patients with a PSMA-specific antibody response had a median overall survival of 46.5 months (95% CI 30.2–62.8), whereas patients without a PSMA-specific antibody response had a significantly shorter median overall survival of 20.6 months (19.0–22.2; p = 0.028). These data suggest that anti-PSMA immunity may contribute to the efficacy of GVAX plus ipilimumab combination therapy and that PSMA seroreactivity is a possible biomarker for clinical benefit [36].

**Summary**

Patients with metastatic CRPC have limited treatment options and a poor prognosis resulting in a requirement for novel approaches to therapy. Augmenting immune responses to prostate cancer is a valid therapeutic approach. Based on the results from a pivotal phase III trial, sipuleucel-T became the first therapeutic vaccine approved for any type of cancer, with additional vaccination strategies also showing clinical activity with minimal toxic effect. A second potential immunotherapeutic strategy for CRPC is T-cell modulation, and following encouraging early-phase results, ipilimumab is now in phase III development.
combination therapy, establishing the optimal combination and sequencing of treatment will prove crucial.

disclosure
The author declares no conflicts of interest.

references
31. Drake CG, Scher HI, Gerritsen WR et al. A randomized, double-blind, phase III trial comparing ipilimumab versus placebo following radiotherapy (RT) in patients (pts) with castration-resistant prostate cancer (CRPC) who have received prior treatment with docetaxel (D). J Clin Oncol 2011; 29(15 Suppl): 27s, Abstr TPS181.
