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Current status of immunological approaches for the treatment of prostate cancer

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Abstract

Purpose of review—The recent Food and Drug Administration approval of sipuleucel-T for metastatic castration-resistant prostate cancer and of the anticytotoxic T-lymphocyte antigen 4 antibody (Ipilimumab) for metastatic melanoma has led to a renewed interest in immunotherapy for prostate and other cancers. Ipilimumab has entered phase III testing for prostate cancer, as has a viral-based anti-prostate-specific antigen vaccine (ProstVac-VF). Complementing these phase III studies are a number of innovative phase II studies, aimed at bringing immunotherapy forward in the setting of less advanced disease, as well as a number of interesting trials combining immunotherapy with conventional therapy for prostate cancer.

Recent findings—Although a number of immunotherapy trials have been initiated, few mature results are available at the current time. These data are likely to mature in the setting of an increasingly complex treatment paradigm in which multiple hormonal and novel agents are available.

Summary—Immunotherapy for prostate cancer represents an attractive treatment approach, with the currently available agent sipuleucel-T providing a significant survival benefit without appreciable toxicity. Novel approaches to improve the efficacy of this and other immune-active agents are currently under evaluation.

Keywords

immune checkpoints; immunotherapy; prostate cancer; T cell; vaccine

INTRODUCTION

Several approaches to immunotherapy for prostate cancer are currently in clinical development. These include agents such as the fully human monoclonal antibody Ipilimumab (Bristol-Myers Squibb, New York, NY, USA), which blocks cytotoxic T-lymphocyte antigen (CTLA) 4 and potentiates an antitumor T-cell response, as well as

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Conflicts of interest

C.G.D. has served as a consultant for Amplimmune Inc, Bristol-Myers Squibb, and Dendreon Inc,. C.G.D. also has stock ownership in Amplimmune Inc. There are no conflicts of interest for E.S.A.

several vaccine constructs involving viral-based and DNA-based products. In addition, a radio-labeled antiprostate-specific membrane antigen (PSMA) antibody is being actively evaluated. Although Food and Drug Administration (FDA) approval of one or more of these agents is possible, the increasingly complex treatment landscape for prostate cancer means that competing treatment options available at the time of potential approval are likely to be very different from the spectrum of agents available today.

DENDRITIC CELL VACCINES

On the basis of a series of phase III trials, including a pivotal 512-patient study [1■■] sipuleucel-T was approved in 2010 for the treatment of metastatic, castration-resistant prostate cancer (mCRPC) [1■■]. Results from that trial showed a statistically significant survival advantage, with men in the active treatment group surviving 25.8 months, as opposed to 21.7 months in the placebo group [hazard ratio (HR) = 0.78, $P = 0.03$]. This result marked the first time that treatment with a cancer 'vaccine' resulted in a survival benefit in a metastatic solid tumor, and was, thus, critically important for cancer immunotherapy. Sipuleucel-T (Dendreon, Seattle, WA, USA) is a personalized, cell-based immunotherapy manufactured using patients' own leukocytes, and is grossly similar to other dendritic cell vaccine approaches [2]. To generate a dose of sipuleucel-T, patients undergo a leukapheresis procedure, and the resulting cells are transferred to one of several processing facilities wherein final product is prepared by incubating enriched monocytes with a proprietary construct that fuses prostatic acid phosphatase (PAP) with granulocyte macrophage colony stimulating factor (GM-CSF). Here, GM-CSF serves to activate and mature the dendritic cells that initiate an immune response, and potentially to direct the PAP protein into these cells [3]. When sipuleucel-T was approved in 2010, men with mCRPC had only a handful of available treatment options. In the timeframe following approval, several additional agents have become available for men with mCRPC; these include the novel hormonal therapy abiraterone acetate (Zytiga, Janssen) [4], as well as the novel taxane cabazitaxel (Jevtana, Sanofi Aventis) [5], both of which demonstrated a survival benefit in men with mCRPC who had progressed on docetaxel chemotherapy. This change in the clinical landscape, as well as increasing awareness that immunotherapy will most likely prove maximally beneficial in the setting of a minimal disease burden [6■] have motivated the initiation of a series of clinical trials aimed at testing the efficacy and feasibility of administering sipuleucel-T in earlier stages of prostate cancer.

Perhaps the earliest stage at which immunotherapy could be used would be prior to primary prostatectomy (Table 1). In this regard, sipuleucel-T was recently administered to approximately 40 men prior to surgery in a multisite phase II trial. This study, (NCT00715104), has completed enrollment; the primary endpoint involves immunological analysis of the prostatectomy specimens. Results are pending at the time of this review. In addition, after primary surgery or radiation therapy, approximately 30–40% of men with prostate cancer present with a rising prostate-specific antigen (PSA) without evidence of overt metastatic disease [7]. This disease state, known as biochemical recurrence, represents a nearly ideal setting for immunological intervention, as the cancer has clearly recurred but disease burden is at a minimum. Men with biochemically recurrent prostate cancer are commonly treated with hormonal therapy (pharmacological castration), although data that

early intervention with androgen ablation results in a significant clinical benefit are somewhat scant [8]. Thus, one combinatorial approach might be to combine androgen ablation with immunotherapy in an effort to modulate PSA kinetics (ultimately, slowing the onset of metastases), or to perhaps initiate an antitumor immune response that could maintain PSA at steady state in the absence of continuing androgen ablation [9]. Preclinical data support this notion, showing that androgen ablation can augment vaccine efficacy [10,11■]. Clinical trial data support this combination as well, including key neoadjuvant studies showing that androgen ablation results in an immunological infiltrate into the prostate gland [12,13]. However, it is not yet clear whether immunotherapy should be administered before androgen ablation (as a ‘priming’ maneuver), or after (serving as an immunological boost). To explore this sequencing issue clinically, a randomized phase II trial has been initiated. In this study (NCT01431391), a standard three-dose course of sipuleucel-T will be administered either 2 weeks before, or 12 weeks into a 12-month course of standard androgen ablation therapy. The primary endpoints of this 60-patient randomized trial will be immune activation related, in an attempt to determine which sequence results in the more robust anti-PAP immune response.

Another key clinical question involves the novel hormonal therapy, abiraterone acetate, which is currently FDA approved for men who have progressed on chemotherapy. A prechemotherapy trial of abiraterone acetate has also been completed, an important clinical question is whether sipuleucel-T should be administered before abiraterone acetate, or concurrently with that agent. To that end, a phase II combination trial has recently been announced. This trial (NCT01487863) will randomize 60 men with asymptomatic or minimally symptomatic metastatic CRPC to receive a standard course of sipuleucel-T followed by abiraterone acetate, or to a regimen in which both treatments are initiated concurrently. Similar to the study in biochemically recurrent disease discussed above, the primary endpoints of this trial will be immunological, but it is certainly conceivable that larger trials with clinical endpoints could follow. One issue in this trial is that abiraterone acetate is generally administered together with continuous prednisone (5 mg twice daily), and the effects of corticosteroid treatment on sipuleucel-T efficacy are currently unknown. Taken together, this series of trials will help to clarify a potential role for sipuleucel-T earlier in the disease course, but larger confirmatory trials with clinical endpoints will likely be required for label expansion purposes.

IMMUNE CHECKPOINT BLOCKADE

The specific T-cell response against cancer can be inhibited by the upregulation of cell surface molecules on activated T cells. These molecules serve as ‘brakes’ to prohibit T cells from proliferating and exerting antitumor effector function [14,15]. The first of these molecules to be evaluated clinically is known as CTLA-4, with the majority of development thus far focused on metastatic melanoma. In a pivotal phase III study, blockade of CTLA-4 with a fully human monoclonal antibody (Ipilimumab, Bristol Myers Squibb) resulted in objective antitumor responses in approximately 11% of treated patients, and a disease control rate of approximately 29% [16■■]. These responses were associated with a survival advantage, and set the stage for FDA approval in early 2011 [17]. Not surprisingly, blocking this critical immune checkpoint results in a significant incidence (approximately 15%) of

grade III and IV autoimmune breakthrough events. In early clinical studies, these side-effects were often serious, and occasionally fatal. However, the recent development of treatment algorithms that prompt rapid immunosuppressive intervention for suspected events seems to have limited the seriousness of these events.

Prompted by the encouraging results in melanoma patients, Ipilimumab has been tested in prostate cancer as well, and a significant number of patients have now been treated in several phase I and II studies. Unfortunately, the clinical and immunological implications of those studies are difficult to interpret, as few of those data have been published. Nevertheless, it does appear that CTLA-4 blockade has some activity in advanced prostate cancer; a 2008 American Society of Clinical Oncology abstract reported a PSA response rate of approximately 23%, with several objective responses [18]. Two randomized phase III trials of Ipilimumab are underway in mCRPC; in the first trial (NCT00861614), patients who have progressed on docetaxel chemotherapy are randomized to low-dose palliative radiation therapy followed by Ipilimumab (10 mg/kg every 3 weeks for four doses) or to placebo. A second trial, (NCT01057810), is enrolling patients with asymptomatic or minimally symptomatic chemotherapy-naive mCPRC, randomizing patients to either Ipilimumab or to placebo. The primary endpoint for both of these trials is overall survival, so mature data are not expected to be available for several years (Table 1).

As is the case for sipuleucel-T, additional trials are focused on using this agent in patients with an earlier stage of disease or in combining immune checkpoint blockade with other therapies. For example, one trial has combined androgen ablation with Ipilimumab in a presurgical setting; preliminary results suggest the potential for meaningful pathological responses at the time of prostate resection [19■]. As discussed above, this particular combination (immunotherapy and androgen ablation) is based on a strong scientific rationale; clinical data from several groups reveal that androgen ablation results in an immunological infiltrate into the prostate gland [12,13]; and both preclinical and clinical data show that androgen ablation may synergize with vaccination in generating a productive antitumor immune response. A recently initiated phase II trial (NCT01377389) will test this combination in the metastatic setting, focusing on androgen-sensitive patients, with a PSA endpoint. In summary, ongoing phase III trials have the potential to lead to approval of Ipilimumab for mCRCP in the next several years, but the overall treatment landscape at that time is far from clear.

VIRAL VECTOR VACCINES

ProstVac-VF (Bavarian Nordic, Washington, DC, USA) is a PSA-directed vaccine approach that has been clinically developed through a series of clinical and basic studies. The current iteration includes a heterologous prime boost (modified vaccinia ankara prime; fowlpox boost), and also incorporates three costimulatory molecules to increase the specific immune response [20]. On the basis of a randomized phase II trial that showed a survival benefit in mCRPC [21■■], an international randomized phase III trial has recently been initiated. This trial (NCT01322490) will enroll 1200 patients and will randomize them to either placebo, ProstVac-VF and subcutaneous GM-CSF, or to ProstVac-VF alone. The primary endpoint of

this trial is overall survival, and enrollment will be limited to men with asymptomatic or minimally symptomatic mCRPC who are chemotherapy naive.

ProstVac-VF has been tested in a number of interesting combination regimens, and several of these combination trials are currently open to enrollment (Table 1). One of these is a phase II combination trial with androgen ablation (NCT00450463); randomizing men with nonmetastatic disease who progress on androgen ablation to either flutamide alone, or flutamide and ProstVac-VF. The primary endpoint of this trial is time-to-treatment-failure, with a secondary endpoint of time-to-metastases. A second ongoing trial will directly test the hypothesis that an anticancer immune response can augment the response to conventional chemotherapy; this hypothesis is supported by copious preclinical data reinforcing the notion that an antitumor immune response is important in the success of standard treatment regimens [22]. This Eastern Cooperative Oncology Group trial (NCT01145508) randomizes men with mCRPC who are chemotherapy naive to either five doses of ProstVac-VF followed by standard docetaxel chemotherapy or to docetaxel chemotherapy upfront. The primary endpoint of this trial is overall survival, with an estimated total enrollment of 144 patients. This is an especially important trial; although the idea that immunotherapy can facilitate a chemotherapy response is well established in preclinical models, well designed combination clinical studies are somewhat lacking.

DNA VACCINES

Vaccines based on specific target antigens encoded in plasmid DNA have several distinct advantages over the approaches outlined above, including ease of manufacture and the flexibility to rapidly evaluate a series of target antigens [23]. The disadvantage of such approaches is their relatively less robust immunogenicity, especially as compared with constructs like the ProstVac-VF product described above. Nevertheless, phase II investigation involving a DNA vaccine encoding PAP (pTVG-HP) showed the induction of a PAP-specific immune response, as well as the suggestion of a decrease in PSA doubling time in a number of patients [24]. One interesting aspect of this study was that specific immune responses took quite some time (several months) to develop in some patients, suggesting the possibility of a more personalized approach, in which some patients might require a longer treatment period than others. A clever phase II trial to test this concept is currently ongoing (NCT00849121) (Table 1). Here, men with nonmetastatic CRPC will be randomized to either a predetermined vaccination regimen (six doses every 2 weeks followed by every 3-months boosting) or to more adaptive vaccine dosing (in which the six dose run-in is followed by either biweekly, monthly, or 3 monthly dosing based on the cellular immune response observed). The primary endpoints of this trial are safety and immune response, but secondary endpoints will include changes in the PSA doubling time, as well as the proportion of patients who remain metastasis free at 1 year. Another somewhat provocative trial compares this vaccine construct against GM-CSF treatment alone, an important clinical question as phase II results show that GM-CSF treatment by itself results in PSA responses in a small percentage of treated patients [25].

PROSTATE-SPECIFIC MEMBRANE ANTIGEN-TARGETED MONOCLONAL ANTIBODIES

The treatment approaches discussed above (vaccines, checkpoint blockade) constitute 'active' immunotherapy, and are thought to function primarily by inducing an adaptive immune response to evolving prostate cancer. In fact, the vast majority of cancer immunotherapy used in the clinic today is not active, but 'passive', involving the administration of high-affinity antitumor antibodies [26]. Anticancer antibody treatment is exemplified by the routine use of trastuzumab in human epidermal growth factor-2/neu-positive breast cancer, as well as rituximab in B-cell lymphoma. In an analogous manner, a high-affinity humanized antibody against PSMA, known as J591, is being developed for prostate cancer [27■]. Early studies with this reagent showed excellent tumor targeting, but a relatively low rate of objective responses. Second-generation development of J591 has focused on radiolabeled constructs, especially those incorporating ^{177}Lutetium [28]. These radiolabeled antibodies proved more promising, and the current version allows simultaneous treatment as well as imaging. Currently, several clinical trials involving ^{177}Lu-J591 are open and actively recruiting patients with various stages of prostate cancer (Table 1).

CONCLUSION

When sipuleucel-T entered phase III clinical studies, there were few treatment options available for men with mCRPC. In general, men with advanced disease were treated with either hormonal therapy or with chemotherapy using docetaxel or mitoxantrone. Of those therapies, only docetaxel was shown to provide a survival benefit in randomized clinical trials [29,30]. In 2011, the range of available treatments for men with mCRPC is far more robust, with the novel taxane cabazitaxel and the novel hormonal therapy abiraterone acetate recently FDA approved. These agents are but a harbinger of things to come, as novel androgen-directed therapies (MDV-3100, ARN-509, TAK-700, TOK-001) and other new agents move through clinical trials in both the prechemotherapy and postchemotherapy settings [31]. This increasingly complex treatment landscape makes trials with a survival endpoint progressively unattractive: This is because, subsequent treatment regimens could potentially confound survival results, leading to a requirement for ever larger trials. Second, survival of men with mCRPC continues to improve, considerably extending the time necessary to complete such studies. In terms of ongoing studies, these considerations are most applicable to the prechemotherapy phase III trials of Ipilimumab and ProstVac-VF; results of these trials will need to be interpreted in the context of a treatment landscape that is probably going to be very different from that encountered in 2012.

In addition, two important clinical questions remain unanswered: First, it is critically important to understand how immunotherapy integrates with hormonal therapy, particularly with the novel antiandrogens and the FDA-approved CYP17 inhibitor abiraterone acetate. This is not a trivial undertaking; the high rate of PSA and objective responses observed using these new agents might make an additive effect of immunotherapy challenging to detect. In addition, the common practice of administering potentially immunosuppressive doses of prednisone along with abiraterone might attenuate the antitumor activity of

immunotherapy. An important consideration in this regard is the relative timing of various treatments: it is not at all clear whether immunotherapy should be given prior to androgen ablation, concurrently with androgen ablation, or after androgen ablation. The ongoing sipuleucel-T/androgen ablation sequencing trial discussed herein could potentially add considerable insight to this question. Second, it seems increasingly unlikely that immunotherapy will be able to compete in this ever-crowded landscape if it cannot produce objective PSA and/or radiological responses. This is because chemotherapy, androgen-directed therapy, and certain novel agents (such as the c-MET inhibitor, XL-184) all seem to induce such responses. Thus, combination regimens [in which immunotherapy is administered in a predetermined sequence (or concurrently) with new and established agents] are likely to be critically important in moving the treatment paradigm forward. Despite these caveats, we must not lose sight of the overall promise of immunotherapy. The significant percentage of Ipilimumab-treated melanoma patients who are alive and off-treatment 5 years after enrollment offers considerable encouragement for clinicians and basic researchers alike to develop treatments and combination regimens that result in long-term, immune-mediated responses.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 257–258).

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KEY POINTS

- Prostate cancer is sensitive to immune treatment, as demonstrated by the survival benefit observed in phase III trials of the autologous cellular immunotherapy sipuleucel-T.
- Several immunotherapy agents, including the immune checkpoint blocking antibody Ipilimumab, and the PSA-targeted vaccine ProstVac are currently undergoing phase III testing.
- Novel hormonal therapies for prostate cancer are advancing quickly in clinical practice, so it is important to understand how hormonal therapy and immunotherapy interact.
- Future development of immunotherapy for prostate cancer will likely focus on earlier stage disease, as well as on logical combinations of immune agents with conventional treatment.

Table 1

Selected prostate cancer immunotherapy agents and trials

Agent	Mechanism/target	Phase III studies	Phase II studies
Sipuleucel-T	Autologous cellular immunotherapy – PAP directed	Completed	Combination with abiraterone acetate (NCT01487863); sequencing with androgen ablation (NCT01431391)
Ipilimumab	Fully human anti-CTLA-4 monoclonal antibody	Prechemo (NCT00861614); postchemo (+ XRT) (NCT01057810)	Neoadjuvant (NCT01194271); combination with androgen ablation (NCT01377389)
ProstVac-VF	PSA-encoding poxvirus prime/boost regimen	Prechemo (NCT01322490)	Sequencing with docetaxel chemotherapy (NCT01145508); combination with flutamide (NCT00450463)
pTVG-HP	PAP-encoding DNA vaccine	N/A	Priming doses followed by personalized versus fixed boost regimen (NCT00849121); comparison with GM-CSF (NCT01341652)
^{177}Lu-J591	Radiolabeled monoclonal antibody to PSMA	N/A	Combination with Docetaxel (NCT00916123); combination with Ketoconazole in nonmetastatic CRPC (NCT00859781); dose escalation study (NCT00538668)

CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; GM-CSF, granulocyte macrophage colony-stimulating factor; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; PSMA, prostate specific membrane antigen; XRT, radiation therapy. For current information, consult www.clinicaltrials.gov.