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From Clinical Trials to Clinical Practice

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Posted: 08/17/2011; Expert Rev Vaccines. 2011;10(6):743-753. © 2011 Expert Reviews Ltd.

Abstract and Introduction

Abstract

Therapeutic options for patients with metastatic castration-resistant prostate cancer are increasing, spurring an urgent need to better understand which treatments are best for individual patients. The recent approval of a first-in-class agent, sipuleucel-T, has intensified this need. This therapeutic cancer vaccine has demonstrated a survival advantage in two Phase III trials, but does not alter progression in the short term. Therefore, a new therapeutic approach for patients with metastatic castration-resistant prostate cancer is taking shape, based on broader understanding of available therapies. This new clinical approach seeks to maximize patient benefit from treatment, minimize associated toxicities, and may have far-reaching implications for other therapeutic cancer vaccines currently in clinical development.

Introduction

More than 6 decades ago, Charles Huggins first identified the androgen receptor as a viable target in the treatment of prostate cancer,[1] and by the end of the century, several targeted hormonal therapies had been developed.[2] The next evolution in prostate cancer treatment began in 2004, when chemotherapy first demonstrated a survival benefit in patients with metastatic disease.[3,4] In recent years, a new generation of hormonal therapies, exemplified by abiraterone, has emerged, and recent Phase III trial results have demonstrated a survival advantage in patients refractory to docetaxel Table 1.[5–7] In 2010, a new type of cancer treatment emerged on the therapeutic horizon – sipuleucel-T (Provenge®; Dendreon Corp., Seattle, WA, USA), an immune-stimulating therapeutic cancer vaccine. Demonstration of a survival advantage in a second Phase III trial of sipuleucel-T in metastatic prostate cancer led to approval by the US FDA.[101]

Table 1. Phase III trials in which sipuleucel-T demonstrated an overall survival advantage relative to placebo.

Study (year)	Population	Patients (n)	Results	Ref.
Small *et al.* (2006)	Metastatic castration-resistant prostate cancer	127 (82 on treatment, 45 on placebo)	Overall survival favored the treatment arm: 25.9 vs 21.4 months (p = 0.01; HR: 1.45)	[15]
Kantoff *et al.* (2010)	Metastatic castration-resistant prostate cancer	512 (341 on treatment, 171 on placebo)	Overall survival favored the treatment arm: 25.8 vs 21.7 months (p = 0.032; HR: 0.78)	[77]

Clinicians must now determine how to incorporate this new class of therapeutics into their practice as sipuleucel-T has advanced from investigational agent to FDA-approved therapy.

Unlike conventional chemotherapy or hormonal therapies, sipuleucel-T requires a different approach because the vaccine does not change short-term disease progression, although it has demonstrated improvement in survival.[8] A review of other modern immune therapies demonstrates that this is probably a characteristic of a new category of agents, and that the strategies developed to use sipuleucel-T may have relevance for other immunotherapy agents in development.[8–10] A general overview of the evolving landscape of prostate cancer therapeutics will help to define the patient population most suitable for treatment with sipuleucel-T. We also provide an overview of an emerging vaccine, PSA-TRICOM, as well as lessons learned from the failed trials of GVAX, a whole tumor-cell vaccine.

Results of Vaccine Clinical Trials

Sipuleucel-T

Sipuleucel-T is a therapeutic cancer vaccine derived from a patient's own immune cells, which are manipulated *ex vivo* to

generate this active cellular product. This agent was developed with the objective of initiating a dynamic immune response targeting prostatic acid phosphatase (PAP), which is expressed by most prostate cancer cells. In order to generate the vaccine, peripheral blood mononuclear cells are obtained from each patient via leukapheresis. Antigen-presenting cells (APCs), such as dendritic cells, collected in this process are enriched by density centrifugation, then pulsed *in vitro* by a PAP–granulocyte–macrophage colony-stimulating factor (GM-CSF) fusion protein. The result of this *in vitro* stimulation is a patient-specific, activated cellular therapy. The entire process (including leukapheresis and *in vitro* stimulation) is repeated three times to allow for a full course of three biweekly treatments.[11,12]

In a Phase I study that demonstrated safety in patients with metastatic castration-resistant prostate cancer (mCRPC), fevers, chills, fatigue and local injection-site reactions were the most common adverse events.[13] In a subsequent Phase I/II study in patients with nonmetastatic castration-resistant prostate cancer (n = 31), sipuleucel-T was infused at weeks 0, 4 and 8. Immune analysis indicated that 38% of patients generated an immune response (in the form of T-cell proliferation) to the PAP fusion protein, and that this response was associated with delayed disease progression. Overall, six patients had a >25% decline in prostate-specific antigen (PSA), three of whom had a >50% decline.[14]

Given these promising preliminary findings, two Phase III placebo-controlled studies were initiated in patients with mCRPC. Randomization for both studies was 2:1 in favor of the sipuleucel-T vaccine, which was administered at weeks 0, 2 and 4. Time to progression was the primary end point of both studies.[15,102] The first Phase III trial enrolled 82 patients on the sipuleucel-T arm and 45 patients on placebo. However, it failed to meet its primary end point of time to progression (which favored sipuleucel-T 16.6 vs 10 weeks; p = 0.052; hazard ratio [HR]: 1.45).[15] Based on these findings, the second Phase III trial was closed prematurely. Again, when the data from 98 enrolled patients were evaluated, no benefit in time to progression was seen.[12,102] Ultimately, however, the secondary end point of overall survival was evaluated on the initial, fully enrolled Phase III trial and demonstrated a 4.5-month improvement favoring sipuleucel-T (25.9 vs 21.4 months; p = 0.01).[15] Since overall survival was not the primary end point of the study, the FDA recommended another Phase III study to confirm the survival advantage. This third and larger Phase III trial enrolled over 500 patients, again randomized 2:1 in favor of sipuleucel-T, and this time overall survival was the primary end point Table 1. Once again, the Phase III study demonstrated a survival benefit with the vaccine (25.8 vs 21.7 months; p = 0.032; HR: 0.78), without changes in time to progression.[8] These results led to FDA approval of sipuleucel-T in April 2010, for patients with minimally symptomatic or asymptomatic mCRPC. Each dose of sipuleucel-T contains a minimum of 50 million autologous $CD54^+$ cells activated with PAP–GM-CSF.[101]

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PSA-TRICOM

Another therapeutic vaccine for prostate cancer that is in late stages of clinical trials does not require *ex vivo* processing of immune cells. PSA-TRICOM (PROSTVAC™), developed by the National Cancer Institute (NCI) and licensed to BN Immunotherapeutics (Mountain View, CA, USA) is a vector-based vaccine that targets PSA through the use of genetically altered poxviruses.[16] Poxviral-based vaccines deliver transgenes for tumor-associated antigens such as PSA to APCs through cellular infection via subcutaneous injections. Once these transgenes have been processed, they are expressed on the APC surface within the MHC, leading to T-cell activation and targeted tumor-cell destruction.[16,17] Poxviral-based vaccines are processed entirely within cellular cytoplasm, so there is no risk of transgenes integrating into human DNA.[17]

A previous Phase II clinical trial demonstrated the merit of a heterologous prime–boost strategy for administering poxviral-based vaccines.[18] In this case, vaccinia and fowlpox, two separate species of poxviruses, were tested and each was found to have merit. Vaccinia initiates a robust immune response, but can stimulate neutralizing host antibodies. Fowlpox does not replicate in humans and so does not stimulate neutralizing antibodies, but can effectively boost an immune response. An evaluation of various sequences of vaccinia and fowlpox found that the optimal schedule employed a vaccinia priming dose

followed by fowlpox boosting doses. On this dosing schedule, 45.3% of patients were PSA progression-free at 19.1 months and 78.1% demonstrated clinical progression-free survival.[18] This same schedule has been employed in subsequent trials of PSA-TRICOM.

PSA-TRICOM also includes transgenes for three T-cell costimulatory molecules, which results in enhanced T-cell activation.[19–21] A Phase I study in patients with mCRPC demonstrated that PSA-TRICOM was well tolerated, with common side effects of mild injection-site reactions, fever and influenza-like symptoms. Four of six evaluable patients demonstrated an increase in the number of PSA-specific T cells after treatment with the vaccine. In addition, nine out of 15 patients had decreases in PSA velocity.[22]

Two Phase II studies with PSA-TRICOM have been completed in mCRPC patients that dosed the vaccine at monthly intervals until disease progression. The larger of the two studies (n = 125) was a placebo-controlled, multicenter trial in patients with a Gleason score of ≤7 and no evidence of visceral metastasis. Randomization was 2:1 in favor of PSA-TRICOM, which was administered via monthly subcutaneous injections. Similar to the sipuleucel-T trials, this study showed no changes in time to progression (the primary end point); however, median overall survival was 25.1 months in the vaccine arm compared with 16.6 months in the control arm, in which patients were given wild-type poxvirus (p = 0.0061; HR: 0.56).[10]

Another Phase II study of PSA-TRICOM was a single-arm trial at the National Cancer Institute (n = 32), which treated patients with mCRPC regardless of Gleason score.[23,103] The median overall survival was 26.6 months, which was similar to the findings of both the larger PSA-TRICOM trial and the sipuleucel-T trials. Immunologic analysis indicated that 13 out of 29 evaluable patients had a >twofold increase in PSA-specific T cells. Patients with the greatest immune response showed a trend toward improved overall survival (p = 0.055).[23,103]

Vaccines Demonstrate Improved Survival but No Benefit in Time to Progression

Both sipuleucel-T and PSA-TRICOM vaccines demonstrate minimal toxicity and a statistically significant overall survival benefit (PSA-TRICOM needs Phase III confirmation) without a short-term change in time to progression, suggesting that this may be a characteristic of this class of therapeutics. It is possible that both vaccines initiate an immune response that has a clinical impact on the tumor only after clinical progression is detected radiographically. Thus, determination of clinical progression in the short term may belie long-term benefits.[24]

The ultimate clinical advantage may be an ongoing immunologic response, which takes time to generate but can be sustained even after the vaccine has been discontinued. Subsequent therapies may enable a greater immune response by increasing cytokine production or immune-enhancing molecular 'danger signals', depleting immunoregulatory mechanisms or enhancing presentation of relevant tumor-associated antigens.[25–27] Combined with the enhanced immune response, patients may have better outcomes on follow-up treatments than would have been expected on standard therapy alone. Although this has not been evaluated prospectively in a clinical trial, an open Eastern Cooperative Oncology Group trial will evaluate docetaxel alone versus vaccine (PSA-TRICOM) followed by docetaxel in men with mCRPC.[104] It should be noted, however, that subsequent therapies may not be necessary to derive clinical benefit from the vaccine.

This phenomenon of survival advantage without improved time to progression is not restricted to therapeutic vaccines for prostate cancer. Ipilimumab is a monoclonal antibody that binds to the CTLA-4 molecule on activated T cells, preventing the immune system's autoregulation of immune responses and ultimately potentiating enhanced antitumor activity by T cells. Early clinical trials established the agent's potential benefit and associated autoimmune toxicities in melanoma.[28,29] A recent Phase III trial in patients with metastatic melanoma demonstrated that patients treated with ipilimumab survived a median of approximately 10 months, compared with 6.4 months for patients who received GP100 as an active control (p < 0.001). This survival advantage was not accompanied by improved time to progression, which was a median of approximately 2.8 months for all enrolled patients.[9]

Mathematical tumor growth models may also provide insight into the altered biology of patients treated with therapeutic cancer vaccines. Based on the mathematical equations developed in several tumor types, tumor growth rates calculated using enlarging tumors on scans, M-spikes in multiple myeloma and levels of serum PSA in prostate cancer may be associated with survival times.[30–33] These calculations show a possible association between disease progression and overall survival. A recent review of prostate cancer clinical trials at the NCI over the last decade demonstrated that these tumor growth models were effective predictors of survival for patients treated with second-line hormonal therapy or chemotherapy, but not for patients

treated with PSA-TRICOM.[30] In a Phase II study of PSA-TRICOM, patients survived longer than their off-study tumor trajectory would have suggested.[33,34] This is another indication that, although disease course may not be significantly altered initially, ultimately, tumor biology or host–tumor interaction may be changed in some patients, perhaps owing to an immune response, resulting in survival time not projected by their relatively short time to progression. While prospective monitoring of therapeutic cancer vaccine trials will be required to validate this hypothesis, these mathematical models seem to corroborate the outcomes seen in several vaccine clinical trials.

Other Treatment Options

Chemotherapy

Despite recent promising advances in the field of immunotherapy, chemotherapy is still the primary treatment for patients with mCRPC, especially those who are symptomatic.[35] Before docetaxel received FDA approval, prostate cancer was considered to be chemo-insensitive, with objective response rates rarely exceeding 10%[36] and the combination of mitoxantrone and prednisone only approved for palliation of symptoms.[36] The landmark trial demonstrating the clinical benefit of docetaxel in mCRPC showed improvement in overall survival by <3 months relative to mitoxantrone and prednisone.[3,4] Reported side effects of docetaxel included myelosuppression, dysgeusia, peripheral neuropathy and fatigue, with 11% of patients having to discontinue therapy owing to side effects. Unfortunately, numerous subsequent studies attempting to develop docetaxel combinations in mCRPC did not enhance the survival benefits seen with docetaxel alone.[37–39]

Attempts to overcome taxane resistance in mCRPC were unsuccessful until 2010. Definitive testing of cabazitaxel, a novel taxane that works by disrupting microtubules, resulting in cell division inhibition and cell death, was recently completed in an international, multicenter, Phase III trial (TROPIC) in patients with mCRPC.[40] Patients with disease progression on docetaxel were randomly assigned 1:1 to receive cabazitaxel plus prednisone/prednisolone (n = 378) or mitoxantrone plus prednisone/prednisolone (MP; n = 377). Results showed an improvement in median overall survival (the study's primary end point) of 15.1 months in the cabazitaxel combination arm versus 12.7 months in the MP arm. Patients who received the cabazitaxel combination also had a significant increase in median progression-free survival (2.8 vs 1.4 months; HR: 0.74; 95% CI: 0.64–0.86; p < 0.0001). Cabazitaxel treatment led to adverse events, especially neutropenia (81.7%), with 18% having to discontinue treatment owing to side effects. The percentage of toxicity-related deaths was higher in the cabazitaxel arm (4.9%) than in the MP arm (1.9%), warranting caution in the use of this agent, especially as a palliative regimen for an older population. Nevertheless, the TROPIC trial showed a clear benefit for cabazitaxel in patients who had previously been treated with docetaxel, resulting in FDA approval for that purpose in June 2010.[105]

Modern Hormonal Agents

While chemotherapy has been used to treat mCRPC, testosterone-lowering androgen-deprivation therapy (ADT) has been the mainstay of treatment for the majority of men who initially develop castration-sensitive nonmetastatic prostate cancer after definitive therapy or have castration-sensitive metastatic prostate cancer at diagnosis.[2] Virtually all men undergoing ADT will eventually become castration-resistant; however, testosterone-lowering agents are continued since androgen receptor signaling probably still plays a role in disease progression in these patients.

Several novel therapeutics targeting cytochrome P17 (CYP17) enzymes have emerged, as well as novel anti-androgens. One such agent, abiraterone, was studied in a Phase I dose-escalation trial involving 21 chemotherapy-naive patients, with doses ranging from 250 mg to 2000 mg across three patient cohorts.[41] Results showed notable PSA declines of ≥30, 50 and 90% in 14 (66%), 12 (57%) and six (29%) patients in the respective cohorts, suggesting antitumor activity with this agent. A subsequent Phase I/II study of abiraterone acetate enrolled 54 chemotherapy-naive CRPC patients, with 42 patients making up the Phase II expansion cohort receiving 1000 mg. This trial again confirmed PSA declines of ≥50% in 28 out of 42 (67%) patients, and PSA declines of ≥90% in eight out of 42 (19%) patients. Radiographic and correlative biomarker responses were also seen. The median time to PSA progression on abiraterone acetate alone for all Phase II patients was 225 days (95% CI: 162–287). In another Phase II study evaluating abiraterone in the post-docetaxel setting,[42] 58 men with progressive mCRPC received 1000 mg/day of abiraterone with prednisone (5 mg twice daily). A ≥50% decline in PSA was confirmed in 22 patients (36%), including 14 out of 31 (45%) ketoconazole-naive and seven out of 27 (26%) ketoconazole-pretreated patients. Phase III data in docetaxel-refractory mCRPC patients has demonstrated an improvement in overall survival of 3.9 months relative to placebo (14.8 vs 10.9 months; HR: 0.65; p < 0.0001).[7] This study led to FDA approval of abiraterone in 2011 for patients with mCRPC who have progressed on docetaxel. A second fully accrued Phase III trial is also evaluating abiraterone in the pre-docetaxel mCRPC setting, with preliminary results expected as early as 2011.[43]

Rationale for Identifying Candidates for Vaccine Therapy in Metastatic Prostate Cancer

The availability of more treatment options brings with it a need to evaluate patients to develop a treatment plan best suited to each individual Table 2. In recent years, many clinicians have employed sequential hormonal therapies until the patient becomes symptomatic, which is generally accepted as the time to initiate docetaxel.[2] Given the toxicity associated with cytotoxic chemotherapy, patients are generally unwilling to endure side effects that may be worse than their disease-related symptoms. The absence of data showing that starting chemotherapy earlier in asymptomatic patients improves outcomes lends further credence to this approach.

Table 2. Relative clinical advantages of therapies demonstrating improved survival in metastatic castration-resistant prostate cancer.

Therapy	Population	Advantages	Disadvantages	Ref.
Docetaxel	Chemotherapy-naive mCRPC patients	May improve symptoms related to mCRPC	Common toxicities include myelosuppression, fatigue, dysgeusia and neuropathyNo clear data suggesting that starting docetaxel earlier in mCRPC leads to better outcomes	[3,4]
Sipuleucel-T†	Chemotherapy-naive mCRPC patients	Minimal symptoms related to therapyBrief course of therapy (1 month)	Lack of intermediate markers of response make it difficult to assess who will do well in the long term | Less likely to be effective in patients with aggressive disease characteristicsProduction of vaccine is labor-intensive	[8]
Cabazitaxel	Post-docetaxel-treated mCRPC patients	Survival benefit after progression on docetaxel	Toxicity profile, including approximately 5% of treatment-related mortalities	[42]
Abiraterone	Post-docetaxel-treated mCRPC patients	Survival benefit after progression on docetaxelLess severe toxicity than cabazitaxelOral administration	Mineralocorticoid-related adverse events in >30% of patients	[7]

†Evaluated in patients previously treated with chemotherapy. However, the authors believe this agent should be used primarily in chemotherapy-naive patients, as discussed in the text.
mCRPC: Metastatic castration-resistant prostate cancer.

The question of how to integrate sipuleucel-T into this conventional schema may be answered, in part, by other vaccine trials. The NCI Phase II trial of PSA-TRICOM retrospectively evaluated overall survival as it related to pretreatment prognostic indicators specified by the Halabi nomogram. This prognostic tool was developed based on an analysis of 1101 mCRPC patients treated in Cancer and Leukemia Group B (CALGB) studies between 1991 and 2001. The nomogram is based on PSA, performance status, lactate dehydrogenase, alkaline phosphatase, hemoglobin, Gleason score, and presence/absence of visceral disease, each of which was found to be a significant predictor of overall survival for patients subsequently treated with second-line hormonal therapy or chemotherapy.[44] Patients from the NCI PSA-TRICOM study were divided into two groups: those with indolent disease (Halabi-predicted survival ≥18 months) and those with aggressive disease (Halabi-predicted survival <18 months). Patients with aggressive disease showed no marked improvement over predicted survival after treatment with PSA-TRICOM (14.6 months actual median survival vs 12.3 months predicted survival). Patients with indolent disease showed a more pronounced improvement in median overall survival, which was not reached at 37.3 months, relative to a predicted median survival of 20.9 months.[23] Although this was a retrospective analysis of a small study, it does suggest that patients with more indolent disease benefit more from therapeutic cancer vaccines. These data are also consistent with the previously discussed tumor growth models, which suggest that vaccines need time to effect changes in tumor growth kinetics.[30–34]

Another example of the benefits of vaccine-based treatments in patients with indolent disease is demonstrated by GVAX, a whole tumor-cell vaccine.[45] Phase II studies of GVAX suggested a clinical benefit for patients with mCRPC. The median overall survival in the cohort receiving the highest dose of GVAX was 35 months, compared with 22 months predicted by the Halabi nomogram.[46] These data led to two randomized Phase III trials at that dose. VITAL-2 compared standard-of-care docetaxel and prednisone versus docetaxel and GVAX in patients with symptomatic mCRPC, but was halted when an interval safety review identified 67 deaths in the docetaxel–GVAX arm versus 47 deaths in the docetaxel–prednisone arm. While vaccine-related toxicity was not the cause of the increased mortality, possible explanations for this outcome included the lack of prednisone in the GVAX arm, or the fact that the whole tumor cells of GVAX secrete GM-CSF, which could influence tumor growth.[39] However, it is also possible that the trial's requirement that patients have symptomatic disease resulted in enrollment of patients with more aggressive disease. Prognostic evaluation with the Halabi nomogram illustrates this point: the median predicted survival of patients in VITAL-2 was only 13 months, compared with 22 months for patients in the Phase II GVAX trial.[39,46] It is interesting to note that the only subgroup analysis to favor the vaccine was in those patients with a Halabi-predicted survival of ≥18 months, for instance, patients with more indolent disease.

There is an immunologic rationale for the better response to a vaccine among patients with indolent disease characteristics. The Halabi nomogram features that suggest indolent disease, as measured by a predicted survival of >18 months, also suggest less tumor volume.[44] High tumor burden has been correlated with an increased number of regulatory T cells and a worse clinical outcome in preclinical models and cancer patients.[47–52] Regulatory T cells may suppress the body's immune response and maintain a self-tolerance to tumor-associated antigens, decreasing a potential response to therapeutic cancer vaccines.[53–57] Furthermore, preliminary data from the NCI trial of PSA-TRICOM showed an association between decreased regulatory T cells (relative to cytotoxic T cells) and enhanced overall survival.[58,59] Future trials could enhance the benefits of a vaccine in mCRPC by combining immunoregulatory cell-depleting agents with vaccine in an effort to overcome tumor-specific immune suppression in patients with higher tumor burden.

Based on the data outlined earlier, the patient population likely to benefit most from sipuleucel-T is mCRPC patients with indolent disease characteristics, minimal symptoms and low tumor burden. Cytotoxic therapy in prostate cancer has generally been reserved for patients with symptomatic metastatic disease, which encompasses a broad category of patients. In the context of this discussion, however, it is important to note that clinical signs, such as pain, may be prognostic. An analysis of 599 patients on three Phase III CALGB trials indicated that patients with high levels of pain had a median overall survival of 10.2 months, while those with low levels of pain had a median overall survival of 17.6 months ($p < 0.001$),[60] suggesting that clinical assessment of patients could help to determine appropriate therapy. In addition to imaging, which provides information on tumor burden, assessment of the magnitude of pain may also be used to determine whether patients receive a vaccine or chemotherapy. Chemotherapy is indicated for patients with higher levels of pain, as it is more likely than vaccine monotherapy to provide symptomatic relief. Furthermore, patients with high levels of pain (a potential indicator of aggressive disease) and an anticipated survival of approximately 10 months may not experience the relatively delayed benefits of vaccine therapy.

Expert Commentary

The earlier discussion makes it clear that the landscape of therapeutics in metastatic prostate cancer is changing, and that consensus on a definitive schedule of therapies is unlikely in the near future. However, now that sipuleucel-T has been approved by the FDA, its potential role in cancer treatment should be discussed with patients as it becomes more generally available (Figure 1).

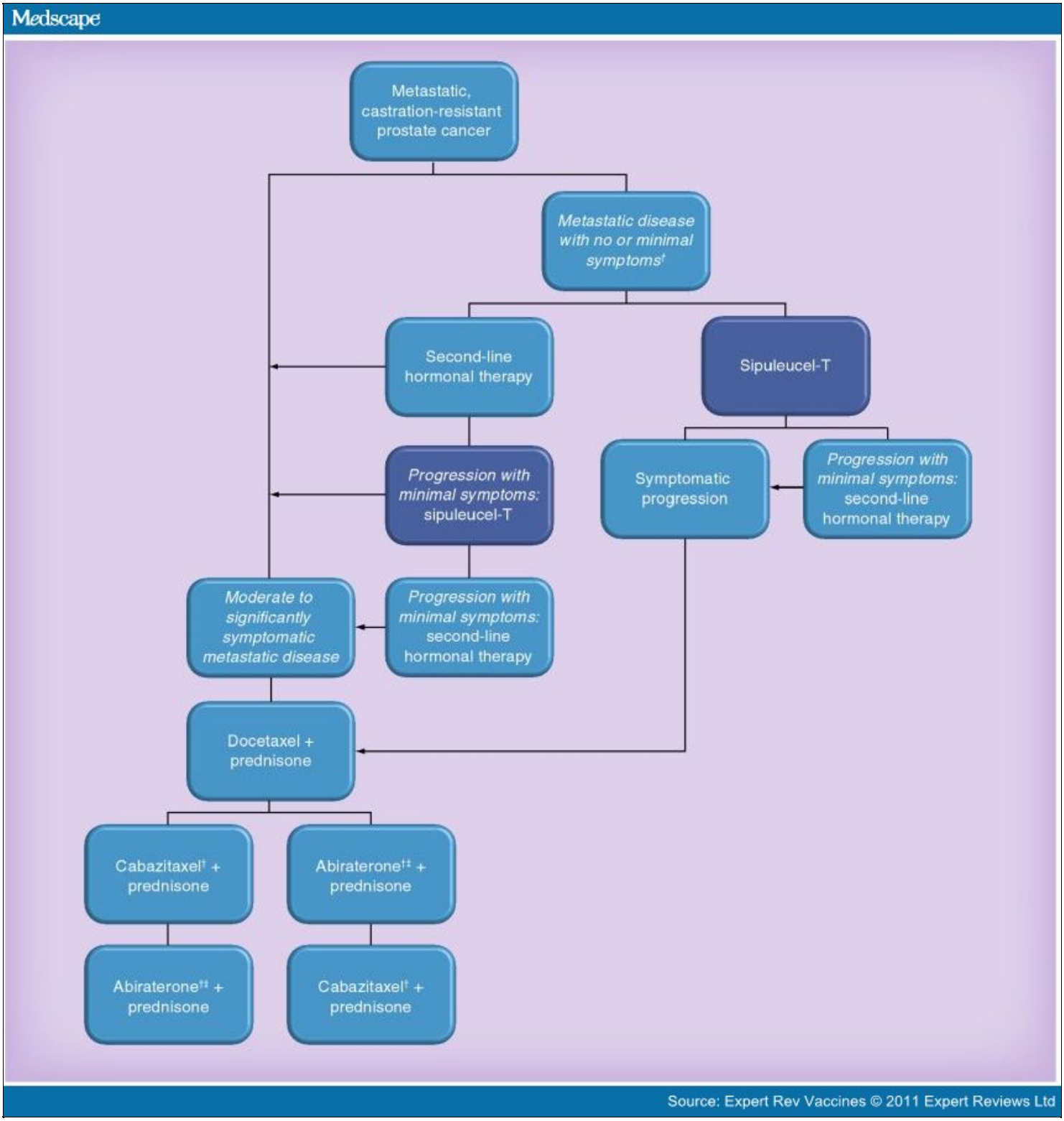

Figure 1. Proposed therapeutic approach to patients with metastatic castration-resistant prostate cancer. Second-line hormonal therapy includes androgen receptor antagaonists and ketoconazole. †For patients with asymptomatic metastatic disease or metastatic patients who have progressed on docetaxel, investigational agents would also be appropriate in the context of a clinical trial. ‡The relative benefits of each sequence of cabazitaxel and abiraterone have yet to be clinically evaluated. Other approaches that could be considered as secondary options under certain circumstances include mitoxantrone and prednisone, estrogens and bone-seeking radionuclides.

Patients With Significant Symptoms

There should be no change in the current clinical approach for patients with newly diagnosed or nonmetastatic prostate cancer. However, metastatic disease calls for a different treatment approach, based on the newly approved agent sipuleucel-T, along

with data showing that the androgen receptor is a viable target even in the postchemotherapy setting.

Current information on the benefits of vaccine-mediated therapy indicates that treating significantly symptomatic patients with sipuleucel-T would not be appropriate. Docetaxel is the most appropriate systemic approach for these patients, given its potential to alleviate symptoms and improve survival. Cabazitaxel's recent FDA approval makes it a suitable option for patients with disease progression post-docetaxel. Recent improvements in overall survival with the use of abiraterone following docetaxel may soon result in FDA approval of this agent. Abiraterone may then prove to be more attractive than cabazitaxel owing to its improved side-effect profile. Additional clinical trials may be required to determine the best sequence of administration for these agents.

Sipuleucel-T is probably best used prior to chemotherapy. The TROPIC trial suggests that the anticipated survival for patients postchemotherapy is 12–15 months.[40] Based on the available data in prostate cancer, this probably represents too short a survival window to benefit from vaccine-mediated therapy.[23,39,46,61] Other vaccine clinical studies also suggest that patients who have been heavily pretreated with recent chemotherapy are less likely to derive benefit from a vaccine.[62]

Patients With Minimal or No Symptoms

For patients with mCRPC who have minimal or no symptoms, chemotherapy is still a viable consideration. However, the practitioner and patient must consider the fact that clinical trials have not shown a clear benefit for chemotherapy administered earlier in metastatic disease. The pace of disease must also be evaluated in this group of patients, as a more rapid pace may limit the effectiveness of sipuleucel-T. However, patients with relatively minimal tumor burden and few symptoms have options beyond chemotherapy and its toxic side effects. Potential therapy for these patients should include both second-line hormonal therapy and sipuleucel-T. Patients who have previously responded to hormonal therapies for 6–12 months or more may benefit from sequential second-line therapies, including androgen receptor antagonists and ketoconazole.[2] Upon progression on such treatments, if patients remain relatively free of significant symptoms, additional hormonal agents or sipuleucel-T could be considered. Should patients develop more symptomatic or rapidly progressive disease (as indicated by rapidly shortening PSA doubling times or increased tumor burden on scans), chemotherapy would be appropriate.[63]

Practitioners who choose sipuleucel-T for this group of patients face the question of what to do next, given that sipuleucel-T is only administered for 1 month and does not alter short-term disease progression. There are several options, but clinicians should bear in mind that the PSA Working Group II recommends not using PSA alone to evaluate for progressive disease,[64] a recommendation that is even more appropriate following vaccine-based treatment that is unlikely to lead to PSA declines. One possibility is to treat such patients with sipuleucel-T and monitor them clinically. Should there be a dramatic change in symptoms or PSA, repeat imaging could evaluate for progressive disease and possible subsequent treatment.

Rising PSA after treatment with sipuleucel-T could lead to consideration of alternative strategies, such as sipuleucel-T followed by second-line hormonal therapy. Such an approach may quell post-sipuleucel-T anxieties without introducing chemotherapy toxicities. Furthermore, as these patients have minimal symptoms, a hormonal approach would be appropriate even if there was minimally symptomatic progression after vaccine treatment. In addition, data in nonmetastatic castration-resistant prostate cancer suggest that vaccine followed by second-line hormonal therapy can lead to improved clinical outcomes.[65] Regardless of the post-sipuleucel-T treatment choice, once patients develop increasingly symptomatic disease progression, chemotherapy is indicated.

Patients With Moderate Symptoms

Patients with moderate symptoms present the greatest dilemma for practitioners, who must also consider tumor burden as a potential indicator of best subsequent treatment. In this context, the prognostic data provided by pain may be helpful.[60] A patient with moderate symptoms who is taking only an NSAID for pain, and has only a few sites of metastatic disease, may still be considered for second-line hormonal therapies or sipuleucel-T. Patients with more advanced disease or who require high doses of pain medication to conduct daily activities are less likely to benefit from sipuleucel-T and may benefit most from chemotherapy. Even so, treatment approaches in this group of patients are likely to vary based on the clinical judgment and experience of the treating physician. Regardless of symptoms or tumor burden, patients should have a comprehensive discussion with their practitioners concerning their prognosis and the anticipated benefits of each treatment option.

Five-year View

Now that a therapeutic cancer vaccine for prostate cancer has emerged, it is likely that similar agents will follow. PSA-TRICOM is the next therapeutic cancer vaccine to enter Phase III testing in 2011, and its 'off-the-shelf' approach would provide logistical advantages over the more labor-intensive sipuleucel-T.[66] Given their favorable side-effect profiles and potential long-term benefits, both of these agents are likely to be used early in the disease process, including in nonmetastatic prostate cancer, and even as part of (neo)adjuvant strategies. It would also be appropriate to evaluate these two agents together, as preclinical data have suggested the benefit of employing multiple vaccine platforms as part of a treatment strategy.[67] Other vaccine formulations such as DNA- and mRNA-based vaccines are also in development and could be added to this equation.[68,69]

Additional approaches will also be evaluated that deploy therapeutic cancer vaccines as part of combination or sequential regimens with other therapeutics, which may enhance the immunologic effects of these vaccines.[25,70] Such studies in prostate cancer will include combinations with standard ADT, chemotherapy, and radiation therapy. Other possible approaches could use nonstandard agents for prostate cancer that have demonstrated immunologic effects, in combination with a vaccine.[71–73] For immunomodulatory purposes alone, such agents could be administered at lower than standard doses, thereby limiting their associated toxicities.

The potential benefits of an anti-CTLA-4 approach will also be explored in mCRPC in both the pre- and post-chemotherapy settings (with radiation). Benefits must be weighed against the potential toxicities of this immunomodulatory strategy.[106] Intriguing preliminary clinical data suggest that a CTLA-4 blockade may enhance vaccine therapy and have a long-term impact on survival.

Ultimately, however, appropriate biomarkers are the key to securing a niche for therapeutic cancer vaccines and other modern immune therapeutics as monotherapies in the treatment of human malignancies. The absence of intermediate markers of response for PSA-TRICOM and sipuleucel-T is likely to be a problem with other vaccines used against cancers. Given the number of patients who will be treated with standard-of-care sipuleucel-T and other vaccines in clinical trials, perhaps, over time, investigators will discover relevant biomarkers or develop improved assessments of immunologic response.[106] Until then, modifications to immunologic therapy-specific parameters for evaluating response, which have already been proposed, may help clinicians to employ modern immunotherapy in their practices.[74]

In the next several years, as providers become more familiar with emerging treatment options for mCRPC, patients will ultimately benefit from diligent, thoughtful consideration of all treatment alternatives. Greater clinical experience with sipuleucel-T, docetaxel and some of the newer agents in late-stage testing (i.e., abiraterone and PSA-TRICOM) will lead to more clearly defined treatment guidelines. In the future, tumor characteristics or genetic polymorphisms may also be used to determine the best therapy for mCRPC.[75,76] Until such parameters are developed, careful clinical assessment is the best way to maximize the benefits of available therapies for patients with mCRPC.

Sidebar

Key Issues

- Sipuleucel-T is the first therapeutic cancer vaccine approved by the US FDA, and is one of several new therapies available for treating metastatic castration-resistant prostate cancer (mCRPC).
- As has been demonstrated by other modern immunologic therapies in clinical testing, sipuleucel-T improves overall survival without short-term changes in disease progression.
- In the absence of biomarkers of intermediate response, careful evaluation of clinical data from trials involving therapeutic cancer vaccines in development may help to delineate a treatment paradigm in mCRPC.
- Vaccine-based therapies are most appropriate for chemotherapy-naive mCRPC patients with no or minimal symptoms.
- Chemotherapy-naive mCRPC patients with moderate-to-severe symptoms or rapidly progressing disease will probably benefit most from standard chemotherapy.
- Future clinical trials will focus on combination studies of therapeutic cancer vaccines and other modalities, and on using vaccines earlier in the disease process.

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Acknowledgements
We thank Bonnie L Casey for editorial assistance in the preparation of this manuscript.

Financial & competing interests disclosure
The authors acknowledge the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research for their support of this study. Jeanny B Aragon-Ching has served on the Speakers' Bureau of Sanofi-Aventis, served on the Advisory Board for Centocor Orthobiotech and has served as an investigator on a research study sponsored by Medivation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

Expert Rev Vaccines. 2011;10(6):743-753. © 2011 Expert Reviews Ltd.