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Immunotherapy for Prostate Cancer: An Emerging Treatment Modality

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Renal cell carcinoma and melanoma have traditionally been thought of as immune-responsive tumors, because rare spontaneous remissions of both tumor types are occasionally observed, and because both tumor types show some degree of responsiveness to nonspecific immunologic stimulation in the form of intravenous interleukin 2 (IL-2).[1,2] Indeed, the prostate gland was originally believed to be immunologically privileged based on a paucity of lymphatic drainage,[3] and animal studies suggest that in the absence of tumorigenesis, the prostate gland is ignored by the immune system.[4] Prostate cancer, however, represents a different immunologic milieu, and several groups showed that prostate tumors contain infiltrating lymphocytes. In some, but not all of these studies, the presence of prostate-infiltrating lymphocytes seems to correlate with improved prognosis.[5,6] In addition, the CD4 and CD8 T cells that infiltrate the prostate gland are oligoclonal in their T-cell receptor sequences,[7,8] suggesting that these cells are responding in a specific manner to their cognate antigen. CD8 T-cell infiltration seems to be more prevalent in prostate cancer than in prostatic intraepithelial neoplasia, again suggesting the likelihood of an ongoing antitumor T-cell response (Gurel and colleagues, unpublished data, 2009).

In light of these observations, it seems possible that prostate cancer might represent a better target for immunologic intervention than previously believed. Other characteristics of the disease contribute to its attractiveness as an immunotherapy target. Perhaps foremost among these is that prostate cancer is initially responsive to hormonal manipulation, and that androgen ablation results in a clear increase in the inflammatory infiltrate in the gland.[7,9] The apoptotic response of prostate cancer to androgen ablation also results in a profound reduction of tumor burden, and a decrease in levels of the immunosuppressive factors associated with bulky disease. Secondarily, although not a perfect tumor maker, circulating levels of prostate-specific antigen (PSA) can be used to guide treatment decisions. In

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addition, the prostate gland is unique among secretory organs, providing various antigens that could be potentially targeted immunologically. Prostate cancer tends to be a slow-growing disease,[10] and the time from initial biochemical relapse to metastatic disease is typically in the range of 7 to 8 years.[11] This extended disease course allows more time for clinical intervention than is available for other tumor types, and also may allow adequate time for a patient's immune system to be sufficiently activated and mediate an antitumor response.

If prostate tumors are infiltrated with CD8 T cells, why then does the immune system not attack and eliminate evolving prostate tumors more frequently? Numerous mechanisms are involved,[12] but one major concern is that the lymphocytes that infiltrate prostate cancer display an exhausted or nonfunctional phenotype. In this respect, the majority (approximately 80%) of the CD8 T cells in the prostate gland express the cell-surface molecule programmed-death 1 (PD-1), which has been associated with a lack of lytic function in several chronic infectious diseases and tumor types,[13] and with poor outcome in renal cell cancer and bladder cancer.[14,15] Antibody-mediated blockade of the PD-1/B7-1 interaction has been shown to restore CD8 T-cell function in human immunodeficiency virus,[16] hepatitis C virus,[17] and in a murine model of chronic infection.[18] Similar results have been observed in animal models of cancer[19] and in cancer-specific human CD8 T cells.[20] So, blocking the interaction of PD-1 and its ligand using a monoclonal antibody restores CD8 T-cell lytic function in several infectious disease and tumor models, and might represent 1 technique by which to augment an antitumor immune response. But many other immunosuppressive characteristics are associated with prostate cancer, including increased circulating levels of transforming growth factor β (TGF-β), which directly suppresses CD8 T-cell activation and function.[21] Other cells in the prostate that potentially downregulate CD8 lytic function include CD4 regulatory T cells (Treg), and immunosuppressive macrophages and myeloid suppressor cells.[22_25]

ACTIVE IMMUNOTHERAPY FOR PROSTATE CANCER

In the past, tumor immunology has generally focused on the concept of activating or educating antitumor lymphocytes, in a manner similar to that used to initiate an immune response against an infectious agent (ie, a vaccine), but this terminology, and the term "vaccine", are probably inappropriate in this context. First, nearly all vaccines for infectious diseases are administered in a preventative setting (ie, in a milieu in which the target antigens [or pathogens] are completely absent). In this context, the immune system has not been previously exposed to the antigens involved, and it is facile to generate a potent, antigen-directed immune response that leads to immunologic memory. In contrast, cancer vaccines are nearly always administered in the context of an evolving or progressive tumor; in this case the immune system has generally been exposed to the target antigen for a considerable time, but has failed to mount an effective response. Thus, cancer vaccines are administered in the setting of ongoing tolerance, a situation in which it is more challenging to generate any response at all, much less a productive immune response leading to long-lasting immunologic memory. For this reason, it is probably more appropriate to refer to approaches designed to activate an immune response against cancer as "immunotherapy," because, like chemotherapy, these approaches are intended to provide therapy for existing

tumors. These stimulatory approaches are generally active in nature, in contrast with the passive administration of antitumor antibodies, which also falls under the broader rubric of tumor immunotherapy. Many immunotherapy approaches have been tested in prostate cancer; these approaches all share the common goal of inducing a specific T-cell response directed against the tumor.[26–29] In the case of the prostate-infiltrating lymphocytes described earlier, the goal of active immunotherapy for prostate cancer is to activate the specific cells preexisting in the gland and to recruit and expand additional pools of tumor-specific lymphocytes that can then traffic to prostate tumors and lyse their targets.

DNA Vaccines

One approach with considerable promise for immunotherapy of prostate tumors involves using DNA-based constructs to activate a specific anti-tumor immune response. This approach was highlighted in a recent study by McNeel and colleagues.[30] These investigators used a DNA vaccine directed against prostatic acid phosphatase (PAP) to treat 22 men with biochemically recurrent prostate cancer (so-called D0 disease). As is nearly always the case for immunotherapy, the treatment was well tolerated, and appeared to result in a T-cell and antibody response to the target antigen. Decreases in the rate of increase of PSA were noted, although the overall clinical significance of such changes is not without controversy. DNA-based immunotherapy vectors are straightforward to synthesize, and this trial therefore provides a foundation on which future trials evaluating additional target antigens may be based.

Viral Vectors: ProstVac VF

Another approach to immunotherapy that has been applied to prostate cancer and other tumor types involves viral vectors, in particular attenuated vaccinia strains. These vectors have the advantage of being capable of incorporating a large target payload, and straightforward synthesis and production.[31] In the context of prostate cancer, a strategy targeting PSA has been systematically developed over the past decade. Because this platform has been extensively reviewed elsewhere,[32] only a few points regarding this agent are discussed in this article. Early in the development of vaccinia-based vectors, it was noted that additional immunization did not seem to result in additional immunity directed against the targeted antigen, but rather at the viral components of the vector itself. Thus, a heterologous prime-boost strategy was designed, in which vaccinia and fowlpox vectors incorporating PSA were synthesized. In a randomized phase II trial, it was shown that vaccinia priming, followed by a series of fowlpox booster treatments, resulted in an optimal immune response as revealed by correlative laboratory studies.[33] Long-term follow-up of that trial has suggested a trend toward increased progression-free survival in men treated with the optimal immunotherapy sequence.[34] An additional refinement to the vaccinia-PSA approach was based on laboratory studies showing that the addition of a triad of costimulatory molecules (B7-1, LFA3, ICAM-1) to the immunizing agent resulted in a significant augmentation of immune responses.[35] The resulting product, ProstVac VF, was partially developed by the Therion Corporation, which launched a 2:1 randomized trial comparing ProstVac VF with placebo in approximately 120 men with asymptomatic, metastatic, castrate-resistant prostate cancer (CRPC) (TBC-PRO-002). Data from this trial were originally presented in 2006, but at that time there was no statistical difference between

the treatment groups in the primary end point (time to progression), or a secondary survival end point.[36] However, long-term follow-up data from these patients were recently presented, and a statistically significant survival advantage was evident, with a median overall survival of 24.5 months in the immunotherapy group versus 16 months in the control group. Because overall survival was a secondary end point in this trial, those data should be considered hypothesis generating. Nevertheless, a phase III trial of this agent is in the planning stages for 2010 initiation (http://www.bavarian-nordic.com/prostvac). In addition to these trials, ProstVac VF has been combined with an impressive number of conventional therapies for prostate cancer, as discussed later. This developmental pathway illustrates several general principles surrounding immunotherapy for prostate cancer. First and perhaps foremost is the slow pace of disease; in the absence of reliable surrogate clinical end point trials take significant time to mature. Secondly, the vaccinia prime, fowlpox boost strategy exemplifies the notion of a heterologous prime-boost immunization scheme (heterologous strategies are rarely used in cancer immunotherapy).

Cell-Based Immunotherapy (GVAX Prostate and Onyvax-P)

A third approach to active immunotherapy for prostate cancer that has proceeded to phase III and phase II randomized clinical trials involves the use of allogeneic prostate cancer cells as immunotherapy vectors. Because cancer cells themselves are generally not sufficiently immunogeneic to mediate protection in murine models, for optimal immunity cancer cells must be either engineered to express a proinflammatory cytokine or administered along with a potent immune stimulator (ie, an adjuvant).[37] The first approach is exemplified by GVAX prostate, which used the cell lines PC3 and LnCaP transfected to secrete GM-CSF.[38] In clinical studies, these cells are irradiated to prevent ongoing division, then injected intradermally. Phase II studies of GVAX prostate were promising,[39,40] and in 2004 a large, randomized phase III trial comparing GVAX prostate with standard docetaxel chemotherapy every 3 weeks in men with minimally symptomatic, metastatic CRPC was launched. This trial, VITAL-1, completed accrual in July, 2007; an interim safety analysis performed in January, 2008 supported trial continuation. A second randomized phase III trial of GVAX prostate was launched in July, 2005; in this trial GVAX prostate was combined with docetaxel to treat men with more advanced disease (ie, patients with symptomatic metastatic CRPC). Although docetaxel chemotherapy is generally administered along with prednisone at a daily dose of 10 mg, prednisone was omitted from the GVAX plus docetaxel treatment arm because of its immunosuppressive properties. The control arm was standard docetaxel combined with prednisone every 3 weeks. This trial (VITAL-2) was halted early because an interim analysis showed an imbalance of deaths in the immunotherapy arm (67 vs 47). The mechanism for this imbalance has yet to be explained, but it did not seem to result from a failure of randomization. Based on these data, an unplanned early futility analysis was designed and completed for the fully accrued VITAL-1 trial.[41] At the time the analysis was conducted, only 371 deaths had occurred, fewer than the prespecified 400 required for 80% power, but the analysis suggested that VITAL-1 had less than a 30% chance of reaching its primary end point of a 20% improvement in survival, and further patient follow-up was halted. The Kaplan-Meier survival curves for VITAL-1 show a clear crossover at 21 months; after this time point patients on the immunotherapy arm show a superior survival. Thus, it remains theoretically possible that further follow-up of these study patients could reveal a

late treatment effect, similar to that seen with ProstVac VF in the TBC-PRO-002 trial. Further clinical development of the GVAX prostate platform has been discontinued by the manufacturer (Cell Genesys Inc). Comparison of the GVAX prostate clinical experience with that of ProstVac VF (TBC-PRO-002) and with Sipuleucel-T (see later discussion) suggests that, in asymptomatic metastatic prostate cancer, a positive result in a randomized clinical trial is more likely when the trial design compares immunotherapy with placebo, rather than with docetaxel chemotherapy. In addition, the unexpected imbalance in deaths in VITAL-2 suggests that combining immunotherapy with other treatment modalities may prove complex, and that randomized phase II trials should be considered before initiating phase III studies.

Another cell-based immunotherapy approach for prostate cancer involves 3 allogeneic prostate cancer cell lines chosen to represent different disease states (Onyvax-P, Onyvax Inc). Specifically, the product includes an immortalized normal human prostate epithelial cell line (ONYCAP23), a transformed cell line from a well-differentiated prostate cancer (P4E6), and the androgen-dependent cell line LnCaP, which was derived from a lymph node metastasis.[42] In clinical trials, the cell lines are first administered as 2 doses of irradiated cells at 2-week intervals along with bacillus Calmette-Guérin as an adjuvant, followed by monthly boosts of the cell lines alone. A phase II trial of Onyvax-P in men with CRPC showed the treatment to be well tolerated and showed a decrease in the PSA velocity in 11 of the 26 patients treated.[43] The current status of Onyvax-P is uncertain, as previously ongoing phase II trials are now closed to accrual (http://www.clincaltrials.gov).

Active Cellular Immunotherapy (Sipuleucel-T)

The active immunotherapy that is most likely closest to approval by the US Food and Drug Administration (FDA) for prostate cancer involves an approach that is different from those described earlier. To manufacture Sipuleucel-T (Dendreon Inc, Seattle, WA, USA), patients undergo plasmapheresis, and a personalized immunotherapy product is produced by culturing a patient's peripheral blood monocytes with a proprietary protein that couples GM-CSF with a target antigen (PAP). This approach has the theoretic advantage of removing antigen-presenting cells (and lymphocytes) from an immunosuppressive patient environment as the cells are activated. In addition, the discrete target antigen facilitates immune monitoring. Phase I and phase III trials of Sipuleucel-T have been reported, with encouraging results.[44–46] FDA approval of this agent is pivotal on a large (>500 patients) randomized placebo-controlled phase III trial (IMPACT), which completed accrual in October, 2007, and which was reported to meet its primary (survival) end point in April, 2009 (http://www.dendreon.com). Thus, when considered along with the TBC-PRO-002 trial of ProstVac VF already described and an earlier phase III trial of Sipuleucel-T (D9901[46]), 3 randomized trials of immunotherapy for metastatic prostate cancer have reported a survival benefit. In all 3 cases the comparator arm was a placebo treatment. Although a placebo comparator might seem unwarranted given that docetaxel chemotherapy every 3 weeks is approved by the FDA for metastatic CRPC in symptomatic and asymptomatic patients, both of these trials enrolled only asymptomatic men, and controversy exists regarding the optimal timing of chemotherapeutic intervention in metastatic prostate cancer.[47]

COMBINING CONVENTIONAL THERAPY WITH ACTIVE IMMUNOTHERAPY

Androgen Ablation

One of the more interesting combination regimens for prostate cancer involves the administration of immunotherapy along with androgen ablation. The clinical rationale for this hypothesis stems from a demonstration of an increased T-cell infiltrate in the prostate glands of men who had undergone androgen ablation before radical prostatectomy.[7] The infiltrating CD4 T cells showed evidence of oligoclonality, suggestive of an antigen-driven immune response. The author obtained similar results in an animal model of prostate cancer, and showed that androgen ablation appeared to mitigate systemic CD4 T-cell tolerance significantly.[4] Further animal studies explored the relative timing of immunotherapy and androgen ablation, and showed that an optimal combinatorial effect is obtained when immunotherapy is administered before androgen ablation.[48] In addition to mitigating T-cell tolerance and promoting T-cell infiltration into the prostate gland, androgen ablation also mediates regrowth of the thymus, the organ in which T cells are produced, and thymic regrowth is accompanied by an increase in T-cell production.[49] Given these considerable data, it is perhaps surprising that more clinical trials have not been performed with this combination.[50] An initial trial was performed by Sanda and colleagues[51] several years ago; ProstVac (without TRICOM or the heterologous prime-boost developed later), was administered to a small number of patients with biochemically relapsed disease. Using a more developed version of ProstVac VF, Madan and colleagues[52] studied sequencing the androgen-receptor antagonist nilutamide in a phase II trial. These results (although derived from only a few patients) mirrored the results obtained by Kast and colleagues in animal studies; patients who received the ProstVac VF vector before secondary androgen manipulation with nilutamide appeared to have an increased survival compared with those who were treated with immunotherapy after androgen manipulation. In the Dendreon P-11 study, men with biochemically relapsed prostate cancer received Sipuleucel-T after androgen ablation. Although final study results have yet to be reported, an initial presentation of these data suggested that this particular combination did not seem to affect the time to PSA recurrence, which was the primary trial end point. Additional clinical trials are warranted, but the results obtained thus far strongly suggest that the precise sequence of the 2 modalities may be of critical importance.

Chemotherapy

Two large phase III randomized controlled trials demonstrated that docetaxel chemotherapy significantly prolongs survival in men with metastatic CRPC,[53,54] and several trials have combined docetaxel chemotherapy with an additional agent in an effort to improve on this documented survival benefit. Agents tested in this manner include anti-angiogenesis agents, mTOR inhibitors, endothelin inhibitors, and others[55]; it followed that immunotherapy might be tested in a similar manner. As discussed earlier, the Cell Genesys VITAL-2 trial compared the combination of GVAX prostate plus docetaxel (without prednisone) with docetaxel plus prednisone in men with symptomatic CRPC, and interim analysis suggested a potential adverse outcome in the men treated with combination therapy. In contrast, a phase II trial comparing docetaxel plus ProstVac VF with ProstVac VF alone showed a prolongation of progression-free survival in the group who received combination treatment,

and found that docetaxel did not seem to impair an immunotherapy-mediated immune response.[56] In addition to combination with standard docetaxel, preclinical and clinical data suggest that low-dose cyclophosphamide may enhance an immunotherapy-induced anti-tumor immune response, most likely through transient depletion of Treg.[57,58] Recent studies by the author's group in an autochronous murine model of prostate cancer confirm these results and reinforce the notion that chemotherapy and immunotherapy must be delivered in a precise sequence for optimal efficacy.[59]

Radiotherapy

Radiotherapy is a conventional methodology for treating localized and recurrent prostate cancer, and several studies showed that radiotherapy has significant proinflammatory effects: upregulation of the proapoptotic molecules Fas and FasL on tumor cells and increasing levels of class I MHC (important for T-cell-mediated tumor lysis).[60] Several preclinical studies directly support the notion of combining radiotherapy for prostate cancer with immunotherapy.[61,62] The combination of active immunotherapy and radiotherapy has been evaluated clinically, once again using the ProstVac VF platform.[63] Thirteen of the 17 patients randomized to the combination radiotherapy/immunotherapy arm in this trial showed an increased T-cell response to the target antigen (PSA), supporting the notion of combining radiotherapy with immunotherapy for prostate cancer. In addition, an ongoing phase III trial of the immune modulator ipilimumab (see later discussion) in patients who have failed docetaxel chemotherapy includes a low dose of radiotherapy in an effort to enhance tumor antigen presentation.

IMMUNE MODULATORS (BRAKES AND ACCELERATORS)

Anti-CTLA4 (Ipilimumab, Tremilimumab)

Although the prostate glands of patients with cancer contain a CD4 and CD8 T-cell infiltrate, phenotypic analyses of these cells[8,64,65] and numerous murine studies[66–70] are consistent with the notion that these infiltrating cells are nonfunctional in lytic function. Several T-cell molecules seem to contribute to this lack of function, most notably CTLA4, which interacts with B7 family molecules on antigen-presenting cells to downregulate T-cell function. In animal studies, CTLA4 blockade was shown to augment an antitumor response initiated by cell-based immunotherapy,[71] and the CTLA4 blocking monoclonal antibody ipilimumab (Medarex Inc, Princeton, NJ, USA) has been evaluated clinically in prostate cancer in several phase I and phase II studies.[72,73] Notably, PSA and radiological responses have been observed following treatment with single-agent ipilimumab, prompting initiation of the multi-institution, randomized phase III trial of this agent described earlier. A study combining anti-CTLA4 with GVAX prostate has also been conducted; initial results were encouraging, suggesting PSA responses in 4 of the first 6 patients treated, with further follow-up accruing.

Additional Brakes and Accelerators (PD-1, OX40)

PD-1 is a cell-surface molecule expressed on activated and exhausted CD8 T cells; expression of B7-H1 (the major PD-1 ligand) in various tumor types is associated with a poor outcome.[13,74] Blockade of PD-1 with a monoclonal antibody augments antitumor

immunity in several murine studies and a phase I trial of a novel, fully human monoclonal antibody specific for PD-1 has completed accrual. This agent was shown to be well tolerated, and clinical responses were observed in several tumor types. The author and others found that most prostate-infiltrating CD8 T cells seem to express PD-1, suggesting that PD-1 blockade might have efficacy in prostate cancer.[8,75] Although limited space does not permit a full discussion in this article, several other cell-surface markers on CD8 T cells are important in activation and initiation of CD8 lytic function, most notably OX40,[76] and several preclinical studies show synergy between OX40 engagement and other antitumor treatment modalities.[70]

MONOCLONAL ANTIBODIES

Anti-PSMA

In several tumor types, monoclonal antibodies directed against cell-surface proteins expressed on cancer cells have had a major effect on morbidity and mortality. Thus, trastuzumab and rituximab (Rituxan) are now standard therapies for patients with Her-2 expressing breast cancer and CD20 expressing lymphoma. Efforts to target prostate cancer cells directly using monoclonal antibody therapy have focused on the cell-surface molecule known as prostate-specific membrane antigen (PSMA),[77] and a modified (human IgG1) monoclonal antibody designated J591.[78] To deliver a cytotoxic payload to prostate tumor cells, this antibody has been conjugated to lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y), two β-emitting radionuclides with distinct properties. ^{177}Lu is a mixed β and γ emitter; the fraction of total energy released as γ irradiation (15%) can be used for imaging with a standard γ camera. In contrast, ^{90}Y is a pure β emitter, and a separate radiolabeled antibody must be used for imaging and dosimetry purposes. ^{177}Lu is a lower-energy β emitter, with an optimal tumor treatment size of 1.2 to 3.0 mm, whereas modeling of the higher energy ^{90}Y shows an optimal tumor treatment size in the 28-to 42-mm range. Because both agents have theoretic advantages and disadvantages, phase I trials in prostate cancer were performed with each. In the ^{90}Y trial, 29 patients with CRPC were treated, and a recommended dose determined.[79] Consistent with the documented specificity of PSMA, metastatic sites were well targeted, and several PSA responses were observed, providing evidence of clinical activity. The ^{177}Lu trial showed similar targeting, and 21 of 35 treated patients had evidence of biologic activity.[80] A randomized phase II trial of ^{177}Lu anti-PSMA in men with non-metastatic prostate cancer has been designed in concordance with the hypothesis that immunotherapy for prostate cancer will prove most successful in patients with a minimal disease burden; this trial is now accruing.

SUMMARY

If Sipuleucel-T is approved for the treatment of metastatic CRPC in 2010, it will be the first antigen-specific immunotherapy to be approved by the FDA for the treatment of solid tumors. This might be viewed as a watershed moment for immunotherapy, and a vindication of prostate cancer as an immune target. From a therapeutic standpoint it is relevant that only a small handful of agents have been approved by the FDA for the treatment of metastatic CRPC, highlighting the significance of the pivotal trial results. In other ways, data from the

potentially pivotal D9902B (IMPACT) trial illustrate some of the hurdles facing the development of immunotherapy. This trial was, of necessity, conducted in the metastatic castrate-resistant setting, a paradox in light of copious experimental data suggesting that immunotherapy is most likely to be efficacious in a setting of minimal residual disease. Moving agents like Sipuleucel-T, ProstVac VF, and others earlier in the disease process is attractive, but hampered by a lack of surrogate end points in prostate cancer that reliably predict survival (or other clinical benefits). In addition, the IMPACT trial used Sipuleucel-T as a single agent, again out of an understandable regulatory necessity. Yet, it is also clear that from significant experimental data that single-agent immunotherapy (much like single-agent chemotherapy) is of incremental benefit in patients with advanced disease. Thus, an obvious future development path for this agent (and others) involves combinatorial approaches administered earlier in the course of disease. The ongoing development of immune checkpoint blocking agents like anti-CTLA4 (ipilimumab, tremilimumab) and anti-PD-1 (Medarex Inc, Princeton, NJ, USA) suggests one route toward combination therapy. Conventional treatments for prostate cancer, especially androgen ablation with its multiple stimulatory immunologic mechanisms, are natural partners for combination with immunotherapy, and several trials combining androgen ablation with active immunotherapy for prostate cancer have been undertaken. Combinations involving radiotherapy and chemotherapy are also supported by preclinical data, but the recent clinical trial experience combining GVAX prostate with docetaxel chemotherapy highlights the importance of completing careful (and perhaps randomized) phase II trials before initiation of larger phase III studies. Despite the inherent complexity involved, the field must move forward with data-driven combination approaches to achieve the ultimate goal of inducing long-term remission in most patients with prostate cancer.

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