Vaccines as Monotherapy and in Combination Therapy for Prostate Cancer

Julia Rotow, Sofia R. Gameiro, Ph.D., Ravi A. Madan, M.D., James L. Gulley, M.D., Ph.D., Jeffrey Schlom, Ph.D., and James W. Hodge, Ph.D., M.B.A.

Abstract

Prostate cancer is the second leading cause of cancer death among men in the United States. Standard-of-care chemotherapy for metastatic castration-resistant prostate cancer is associated with significant but modest survival benefit, indicating a need for alternative and/or additional approaches. The use of therapeutic cancer vaccines for the treatment of prostate cancer represents a novel targeted therapeutic approach. Whereas vaccine strategies are being developed for the treatment of various stages of prostate cancer, this article focuses on novel vaccine strategies for castration-resistant prostate cancer that have been translated into late-stage clinical studies.

Keywords: prostate cancer, immunotherapy, poxviral vaccines, radiation

Therapeutic Cancer Vaccines

Therapeutic cancer vaccines constitute a potential emerging modality for the treatment of a wide range of human malignancies, including prostate cancer. Areas of intense investigation include the development and characterization of (a) tumor-associated antigens (TAAs) or tumor-specific antigens selectively expressed or overexpressed by tumor cells relative to normal adult tissues; (b) novel vaccine delivery systems for the induction of endogenous host antitumor immune responses; (c) cytokines and other immunostimulatory molecules to further amplify the immunogenicity of vaccine formulations; and (d) approaches employing dendritic cells (DCs) expressing relevant tumor-rejection antigens or effector cells which activate or mediate antitumor responses, respectively.

Rationale for Vaccine Therapy in the Treatment of Prostate Cancer

Prostate cancer is the most prevalent solid tumor malignancy among men in the United States, accounting for over 192,000 new diagnoses, resulting in approximately 27,000 deaths in 2009 alone.[1] Despite local therapy, up to 40% of patients develop recurrent disease initially characterized by elevated levels of prostate-specific antigen (PSA). Upon relapse, androgen ablation is only temporarily effective, secondary to the development of prostate cancer cells that are able to grow in spite of castrate levels of testosterone.[2] Ultimately, patients develop overt metastatic disease, with current treatment options including secondary hormone therapy, chemotherapy, and investigational agents. Docetaxel is the only chemotherapeutic agent shown to lengthen overall survival (OS) (by approximately 2–3 months) in men with metastatic castration-resistant prostate cancer (mCRPC).[3] Although approval of docetaxel by the US Food and Drug Administration (FDA) in 2004 represented a significant milestone in the treatment of prostate cancer, alternative therapeutic strategies with more favorable toxicity profiles are highly sought after for the management of patients with disease progression. Prostate cancer patients often present with low tumor burden and good performance status and are therefore ideal candidates for vaccine therapy.

Prostate-Specific Tumor-Associated Antigens as Targets for Immunotherapy

The ideal targets for vaccine-mediated immune responses are TAAs that are overexpressed in, or unique to, cancer cells relative to nonmalignant tissue. Prostate cancer cells express several of these TAAs. PSA is a 34-kD protein uniquely expressed in prostate cancer cells and in nonessential epithelial cells within the prostate, making it the main target for numerous prostate cancer vaccines.[4,5] Prostate-specific membrane antigen (PSMA) is a 100-kD transmembrane glycoprotein mainly expressed in primary and metastatic prostate cancer cells.[6] This TAA is unique in that its expression is augmented by androgen deprivation, a fundamental treatment for prostate cancer.[7] Another potential target for vaccines is prostatic acid phosphatase (PAP), a 102-kD TAA glycoprotein expressed on over 95% of prostate cancer cells and believed to be associated with disease progression.[8,9]

Vaccine Strategies

At this writing, no therapeutic cancer vaccine has been approved by the FDA. However, recent evidence indicates patient benefit with the use of several new cancer vaccines and vaccine strategies for prostate cancer, either as monotherapy or combined with conventional therapeutic regimens.[10–12] Promising results in several clinical studies with various vaccine platforms in prostate cancer have led to ongoing or planned phase III trials (*Table 1*).

Vaccine as Monotherapy

An innovative approach to vaccine therapy relies on antitumor responses elicited by autologous DCs following *ex vivo* loading and stimulation with an antigen. The DC vaccine sipuleucel-T (Dendreon Corp., Seattle, WA, USA) consists of autologous DCs activated *in vitro* with a fusion of the TAA PAP and granulocyte-macrophage colony-stimulating factor (GM-CSF) following leukapheresis. Three phase I/II studies have demonstrated the safety and efficacy of this strategy in metastatic and nonmetastatic CRPC.[13–15] An initial phase III placebo-controlled study was completed in patients with mCRPC with time to progression (TTP) as primary endpoint (*Table 1*). Results indicated a trend to improved TTP in patients treated with vaccine relative to placebo ($p = 0.052$). Although this trial failed to meet its primary endpoint,

Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA
Correspondence: J Schlom (js141c@nih.gov)

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Vaccines as monotherapy						
Cancer stage	**Vaccine type**	**Comment**	**Trial phase**	***n***	**Outcomes**	**Ref.**
Metastatic CRPC	Dendritic cell	Autologous PBMC activated with a PAP-GM-CSF fusion protein	III	512	25.8-month median survival on vaccine arm vs. 21.7 months on placebo arm. Overall 22.5% reduction in risk of death (HR 0.775, $p = 0.032$).	43
Metastatic CRPC	Dendritic cell	Autologous PBMC activated with a PAP-GM-CSF fusion protein	III	127	Median survival of 25.9 months on vaccine arm vs. 21.4 months on placebo arm ($p = 0.01$).	16
Metastatic CRPC	Allogeneic whole tumor cell	Two irradiated prostate cancer cell lines engineered to express GM-CSF	III	626	Overall survival of patients receiving vaccine was similar to patients receiving standard of care docetaxel.	20
Metastatic CRPC	Viral vector	rV/rF-PSA-TRICOM	II	125	Median survival of 25.1 months on vaccine arm vs. 16.6 months on placebo arm (HR 0.56, $p = 0.0061$)	12
Metastatic CRPC	Viral vector	rV/rF-PSA-TRICOM	II	32	26.6-month median survival with vaccine vs. 17.4-month predicted survival	36
CRPC	Allogeneic whole tumor cell	Three irradiated prostate cancer cell lines with BCG adjuvant	II	52	Patients without bone metastases ($n = 26$): Those with declining PSAV post-vaccination (42%) had median TTP of 58 weeks vs. historical 20–29 weeks. Patients with bone metastases ($n = 13$): Those with declining PSA post-vaccination (23%) had a median TTP of 23 weeks vs. historical 9–16 weeks.	17,65
Metastatic CRPC or localized recurrent disease	Dendritic cell	Autologous dendritic cells pulsed with 2 PSMA peptides	II	62	Patients with clinical response (30%) had median TTP of 144 days (metastatic cohort) and 184 days (local recurrence cohort).	66,67
Vaccines in combination with conventional therapies						
Cancer stage	**Vaccine**	**Conventional therapy**	**Trial phase**	***n***	**Outcomes**	**Ref.**
Metastatic CRPC	Dendritic cell: autologous PBMC activated with a PAP-GM-CSF fusion protein	Docetaxel	III	225	Integrated analysis of patients receiving docetaxel in two identical phase III trials. Median survival with docetaxel post-progression on vaccine ($n = 51$) was 34.5 months vs. 25.4 months with docetaxel post-progression on placebo ($n = 31$) (HR 1.9, $p = 0.023$).	44
Metastatic CRPC	Viral vector: rV-PSA/rV-B7-1 prime/ rF-PSA boost	Docetaxel	II	28	Equivalent increase in PSA-specific T cells post-vaccination with and without docetaxel. Patients treated with docetaxel after progression on vaccine ($n = 11$) showed longer TTP on docetaxel (6.1 months) vs. historical controls (3.7 months).	45
Biochemical failure post prostatectomy	Liposome MUC-1	Cyclophosphamide	I	16	50% of patients had stabilization of PSA	68
Localized prostate cancer	Viral vector: rV-PSA/rV-B7-1 prime/ rF-PSA boost	Radiotherapy	II	30	76.5% of patients in the combination therapy arm showed ≥3-fold increase in PSA-specific T cells vs. 0% with radiotherapy alone ($p < 0.0005$).	61
Non-metastatic CRPC	Viral vector: rV-PSA/rV-B7-1 prime/ rF-PSA boost	Nilutamide	II	42	Median overall survival for patients on nilutamide after progression on vaccine was 6.2 years vs. 3.7 years for patients on vaccine following progression on nilutamide ($p = 0.045$).	11

PBMC = peripheral blood mononuclear cell; PSAV = prostate-specific antigen velocity.

Table 1. Prostate cancer vaccines in late-stage clinical trials.

there was statistically significant improvement in median OS with vaccine (25.9 months in the treatment arm vs. 21.4 months on placebo; $p = 0.01$).[16] The results of a definitive randomized, controlled study with sipuleucel-T were recently presented.[17] In this study, there was a statistically significant and clinically meaningful improvement in OS (25.8 months vs. 21.7 months; $p = 0.032$) in patients receiving vaccine compared with those receiving placebo.

Allogeneic whole tumor cell vaccines are vaccines utilizing tumor cell lines, often engineered to express cytokines and thus become more immunogenic. GVAX (Cell Genesys, Inc., San Francisco, CA, USA) consists of two prostate cancer cell lines (LNCaP and PC-3) engineered to express GM-CSF at the vaccine site (*Table 1*). In a phase II study, the median survival for patients with metastatic disease ($n = 34$) was 26.2 months, more than 6 months longer than the median survival predicted for each

group by the Halabi nomogram.[18] Based on these encouraging data, a multicenter, randomized, controlled phase III trial (VITAL-1) was designed to compare OS of asymptomatic metastatic prostate cancer patients treated with GVAX to those treated with docetaxel plus prednisone. VITAL-1 completed recruitment of 626 patients in July 2007. Possibly because of the trial design (randomized potentially to chemotherapy), the patients enrolled on this study had more advanced disease than those enrolled on the phase II studies.[19] Because of data obtained from another study, the company did a non-pre-specified futility analysis and found that the OS of patients treated with GVAX was similar to those patients treated with docetaxel (hazard ratio [HR] 1.03), and with significantly less toxicity associated with vaccine. In addition, in the subgroup of patients with a Halabi nomogram predicted survival of > 18 months, there was a trend toward improved survival in patients randomized to treatment with vaccine compared to patients treated with docetaxel (HR 0.9).[20] As VITAL-1 was not designed to show noninferiority, the trial was terminated in 2008 after a futility analysis showed only a 30% chance of demonstrating a survival benefit. Since these data are relatively immature with only 371 deaths having occurred in 621 enrolled patients at time of initial reporting, further follow-up is planned.[20] Because patients with a longer predicted survival tended to have a greater improvement in survival compared with chemotherapy alone, it is possible that further follow-up may show even more advantage to vaccine.

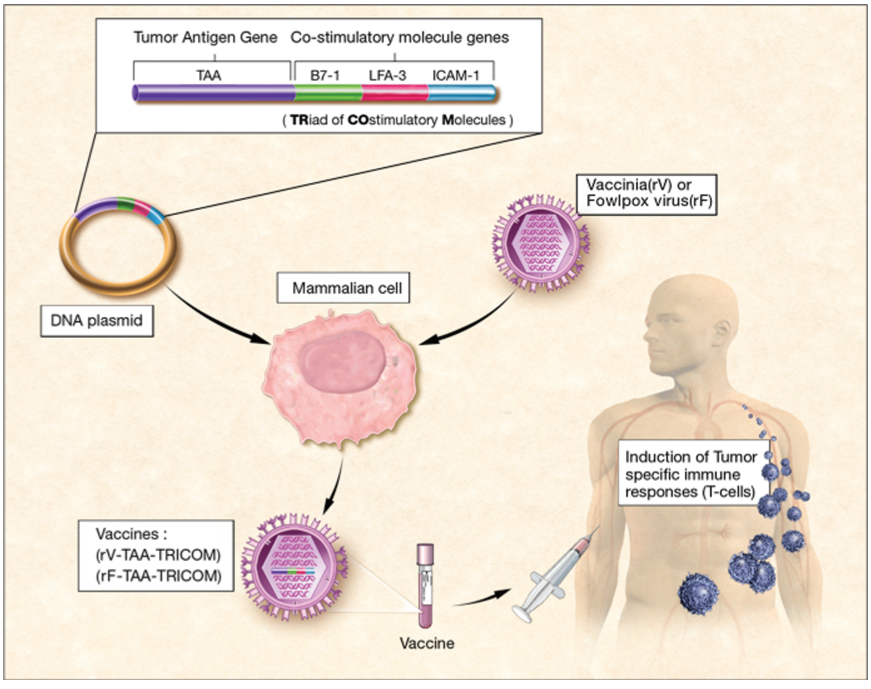

Figure 1. Recombinant vaccinia (rV) or recombinant fowlpox (rF) engineered to express both TAAs and a TRIad of COstimulatory Molecules (B7-1, ICAM-1, and LFA-3) (TAA-TRICOM) can induce tumor-specific immune responses in both preclinical and clinical settings.

An alternative approach consists of vaccine strategies to enhance the host immune response to TAAs. Recent advances in these strategies have enhanced vaccine therapeutic efficacy and include (a) identification of new TAAs or modification of known TAAs to optimize epitope presentation to cytotoxic T lymphocytes (CTLs); (b) concurrent delivery of multiple costimulatory signals to augment the generation of tumor-specific T-cell responses; (c) use of diversified prime-and-boost regimens where patients are primed with a recombinant TAA encoded by recombinant vaccinia (rV) virus and boosted multiple times with a related nonreplicating recombinant fowlpox (rF) virus; and (d) combination of cancer vaccines with conventional therapies.

Early studies with rV-PSA demonstrated that poxvirus vaccines enhance PSA-specific immune responses.[21–24] Further, immune responses were augmented by incorporation of both vaccinia and avian poxviruses in a diversified prime-and-boost regimen.[22,24,25] These preclinical findings provided the basis for the use of vaccinia prime/fowlpox boost strategies in current clinical trials.

A second critical aspect of vaccine design is the delivery of strong costimulatory signals for effective T-cell activation. Preclinical studies[26–30] have demonstrated the advantage of using poxvirus vaccines containing the transgenes for three T-cell costimulatory molecules (TRICOM) along with the TAA transgene, compared to vaccines containing either one or no costimulatory transgenes (*Figure 1*). This advantage was defined by both increases in T-cell responses to the TAA and by antitumor responses. Furthermore, increasing costimulatory signals via TRICOM generates higher-avidity CTLs and memory T cells.[30–33] Preclinical studies in tumor-bearing mice transgenic for the human carcinoembryonic antigen (CEA-Tg) treated with rV/rF-CEA-TRICOM showed significantly improved survival relative to mice receiving rV/rF-CEA or to control animals.[29]

These preclinical findings provided the rationale for clinical translation of rV/rF-PSA-TRICOM, a prostate cancer vaccine now in late-stage clinical studies. rV/rF-PSA-TRICOM is a vector-based vaccine delivered in a heterologous prime-and-boost regimen as an initial priming dose of vaccinia recombinant for PSA-TRICOM (rV-PSA-TRICOM) followed by boosts with rF expressing the same four transgenes (rF-PSA-TRICOM).[12,34] Two concurrent phase II clinical studies have demonstrated the clinical potential of rV/rF-PSA-TRICOM in patients with metastatic prostate cancer (*Table 1*). One recent study was a randomized, placebo (empty vector)-controlled, multicenter trial in patients (n = 125) with progressive metastatic disease despite castrate testosterone levels and a Gleason score of ≤7.[12,35] Patients with visceral disease or a history of chemotherapy or narcotic use were excluded. Although the study did not meet its primary endpoint of progression-free survival, vaccinated patients had a greater 3-year OS rate than control patients (30% vs. 17%), and a longer median OS (25.1 vs. 16.6 months; estimated HR 0.56; 95% CI 0.37–0.85) (*Figure 2*). The vaccine was well tolerated and associated with a 44% reduction in the death rate and an 8.5-month increase in median OS over patients treated with placebo (p = 0.0061).[12]

A concurrent multicenter, randomized phase II trial employing rV/rF-PSA-TRICOM vaccine also provided evidence of enhanced median OS (p = 0.0061) in patients with mCRPC.[36] In this study, 32 patients were vaccinated with rV/rF-PSA-TRICOM in a diversified prime-and-boost regimen (*Figure 3*). No exclusion criteria for visceral disease or narcotic use were applied. While Gleason score has traditionally been

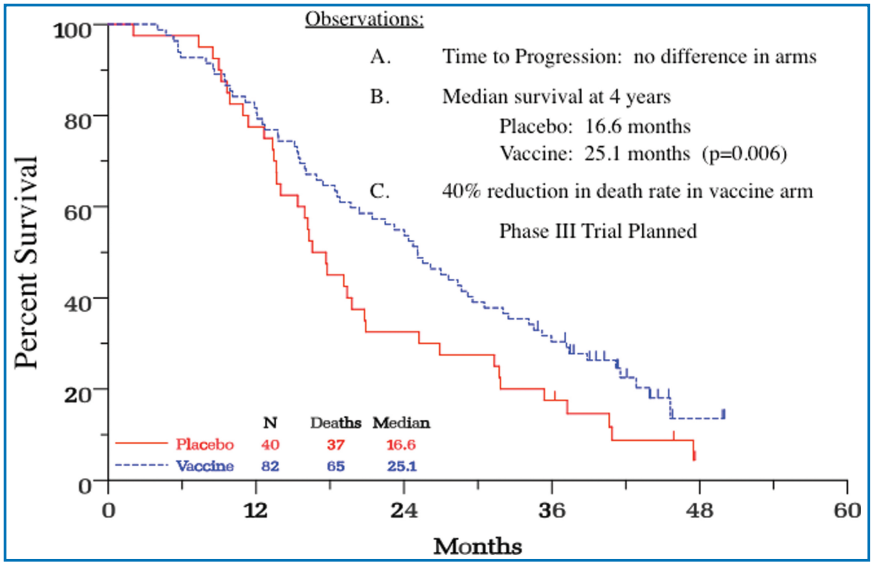

Figure 2. Overall survival (OS) analysis of a phase II, randomized, controlled trial of a poxviral-based PSA-targeted immunotherapy in mCRPC. Graphs indicate the Kaplan-Meier estimator for vaccine (blue) and control (red) arms. Vertical ticks indicate censoring times. Taken from Reference 12.

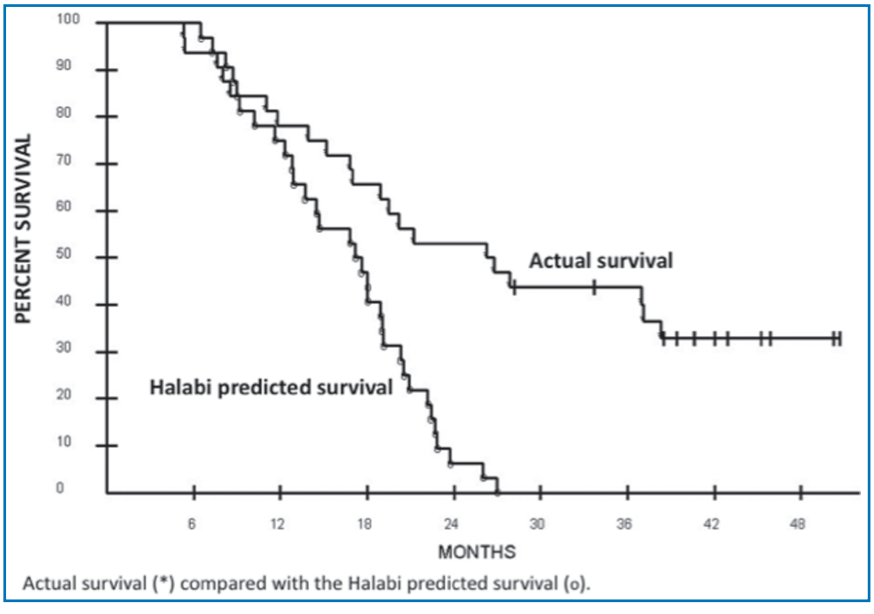

Figure 3. Overall survival analysis of a phase II study of PSA-TRICOM in the treatment of mCRPC. The Kaplan-Meier curve for all 32 patients enrolled demonstrates a median survival of 26.6 months and a median Halabi predicted survival of 17.4 months. Taken from Reference 36.

a main prognostic indicator for localized prostate cancer, this trial stratified patient responses retrospectively using the Halabi nomogram,[37] a tool that can be used to predict OS in patients with mCRPC. The Halabi nomogram is a pretreatment prognostic model derived from results of six separate Cancer and Leukemia Group B (CALGB) trials of 1,101 patients with mCRPC, which predicts OS based on seven baseline prognostic factors: lactate dehydrogenase, PSA, alkaline phosphatase, Gleason score, Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin, and presence of visceral disease. Following vaccination with rV/rF-PSA-TRICOM, declining serum PSA and index lesion size were observed in 37.5% and 16.7% of patients, respectively. The median OS was 26.6 months (vs. 17.4 month median survival predicted by the Halabi nomogram) with a trend toward increased survival in those with a greater than six-fold increase in PSA-specific T cells ($p = 0.055$). Stratification of the results by Halabi predicted survival showed the most benefit in patients with more indolent disease (*Table 2*). Patients with a predicted survival of less than 18 months (median 12.3 months) had an actual median OS of 14.6 months, while those with predicted survival of 18 months or more (median 20.9 months) will reach at least 37.3 months median OS ($p = 0.035$).[36]

These provocative studies provide preliminary evidence of clinically meaningful benefit and have resulted in the design of a confirmatory randomized, double-blind, placebo-controlled phase III trial in patients with mCRPC to begin in 2010.

Vaccine and Chemotherapy

Docetaxel is among the most widely used chemotherapeutic agents for carcinoma therapy and is the only FDA-approved agent for metastatic prostate cancer.[3] The traditional goal of chemotherapeutic regimens has been to induce direct cytotoxicity and tumor cell death. However, certain chemotherapeutic agents including docetaxel have been shown to also modulate the expression of immune-relevant proteins in the tumor cell as well components of the host immune system which can be advantageous for vaccine-mediated antitumor activity.[38–42] Recent evidence from two placebo controlled randomized phase III trials with Sipuleucel-T suggest clinical benefit for patients

	All patients ($n = 32$)	Patients with Halabi predicted survival < 18 months	Patients with Halabi predicted survival ≥ 18 months
Predicted survival by Halabi score (months)	17.4	12.3	20.9
Actual median overall survival (months)	26.6	14.6	Not reached (≥ 37.3 months)
Difference (months)	9.2	2.3	≥ 16.4
Patients, survival longer than predicted by Halabi nomogram	22 of 32 (69%)	10 of 17 (59%)	12 of 15 (80%) p = 0.035

Table 2. Vaccination of patients with PROSTVAC-V/F. Survival predicted by Halabi nomogram versus actual overall survival. Taken from Reference 36.

receiving docetaxel post-vaccination.[10,16,43] Patients with asymptomatic mCRPC were randomly assigned in a 2 to 1 ratio to receive vaccine (n = 147) or placebo (n = 78). Although the primary endpoint of these studies—progression-free survival—did not achieve statistical significance, of great interest, however, is the finding that patients who subsequently received docetaxel chemotherapy showed increased survival if they had received prior vaccine therapy rather than placebo.[17,44]

In the preclinical setting, docetaxel has been shown to modulate $CD4^+$, $CD8^+$, $CD19^+$, NK, and Treg populations in nontumor bearing mice.[40] Further, these studies demonstrated that docetaxel provides optimal enhancement of antigen-specific T-cell responses to recombinant viral vaccines when administered after vaccination, resulting in increased tumor-derived cascade antigen responses and reduced tumor burden. These studies have translated into clinical trials in patients with metastatic CRPC and rising PSA using rV- and rF-PSA. A randomized phase II study combining standard docetaxel chemotherapy with rV-PSA and a vector containing a single T-cell costimulatory molecule (rV-B7-1) followed by 7 monthly boosts with rF-PSA in patients with mCRPC has been completed. Patients received either vaccine alone or vaccine plus docetaxel.[45] Chemotherapy did not appear to blunt the immune response, as both cohorts demonstrated similar increases in PSA-specific T-cell precursors. Recent poxviral studies have added multiple costimulatory molecules to both priming and boosting vaccines.[46] A multicenter randomized Phase II trial has now been approved by ECOG and CTEP (NCI) in patients with metastatic prostate cancer. Patients will be randomized to either docetaxel, or rV/rF-PSA-TRICOM (PROSTVAC) vaccine followed by docetaxel. These PSA-TRICOM vaccines are showing evidence of clinical benefit in terms of enhanced survival compared with predicted survival in patients with metastatic CRPC.[47]

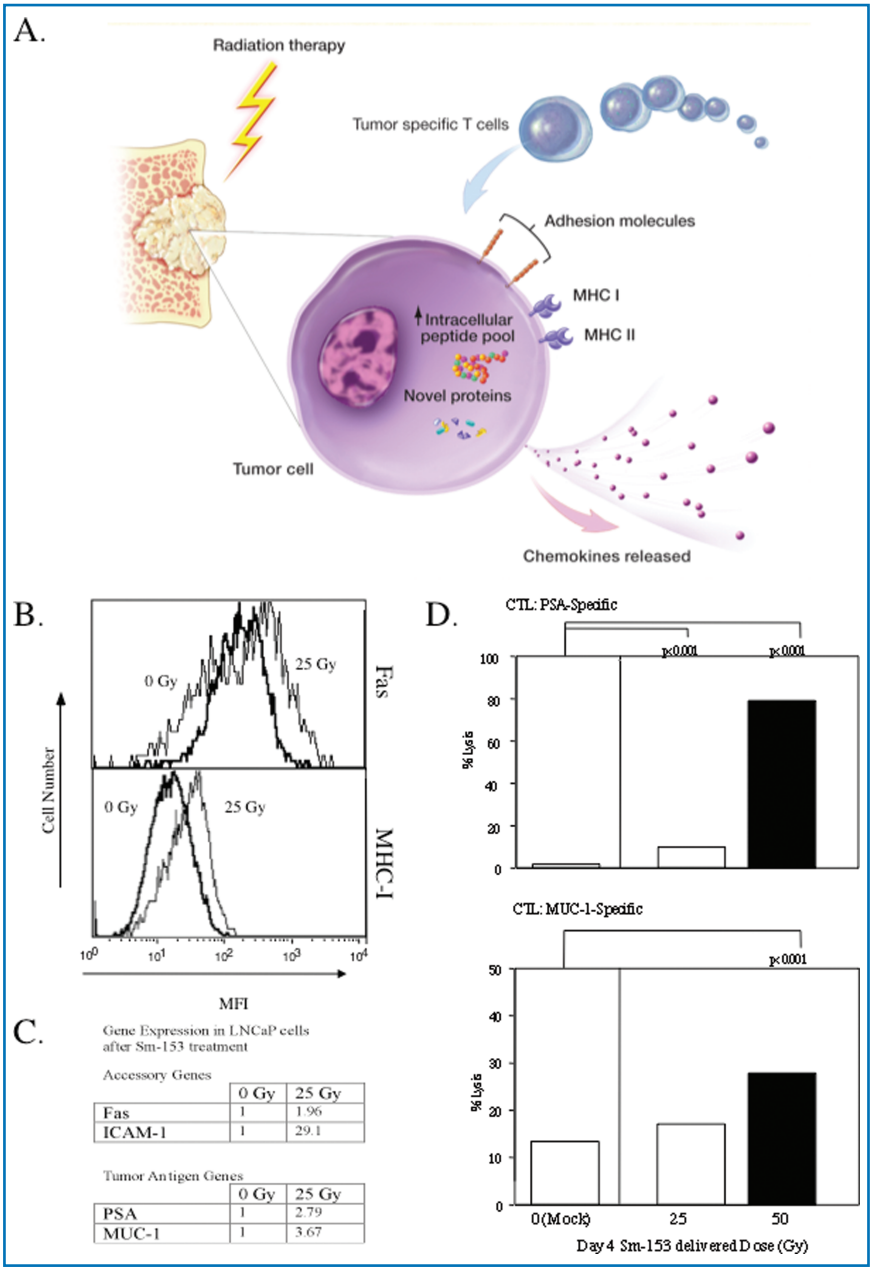

Figure 4. (A) Irradiation modulates tumor-cell phenotype and increases immune recognition. Irradiation can cause (1) upregulation of chemokines and adhesion molecules, providing signals for T cells to come to areas of tumor, (2) upregulation of MHC molecules and TAAs, making it easier for T cells to recognize tumor, and (3) upregulation of Fas and downregulation of regulatory T cells, making it easier for cytotoxic tumor-specific T cells to kill tumor. (B) Upregulation of MHC class I and Fas on prostate cancer cells after exposure to ^{153}Sm-EDTMP. LNCaP cells were exposed to 0 Gy (heavy line) or 25 Gy ^{153}Sm-EDTMP (thin line) over 4 days. Cell-surface expression of MHC class I (bottom panel) and Fas (top panel) was measured by flow cytometry (MFI = mean fluorescence intensity). (C) Upregulation of accessory and tumor antigen genes following exposure to ^{153}Sm-EDTMP. LNCaP cells were treated with 0, 25, or 50 Gy ^{153}Sm-EDTMP. At 48 hours, RNA was extracted from treated cells and quantitative real-time PCR was performed on indicated genes and normalized against the housekeeping gene GAPDH. Numbers depict fold increase compared with the 0 Gy sample. (D) Effect of ^{153}Sm-EDTMP on sensitivity of LNCaP cells to antigen-specific CTL killing. LNCaP cells were exposed to 0, 25, or 50 Gy ^{153}Sm-EDTMP. Cells were harvested 72 hours after exposure and labeled with ^{111}In. CTLs specific for PSA or MUC-1 were incubated with labeled LNCaP cells at an E:T ratio of 30:1. After 18 hours, supernatant was harvested and specific lysis was calculated. Taken from Reference 64.

Vaccine and Radiation

Radiation is standard therapy for prostate cancer, primarily for local tumor control via direct cytotoxicity. Although local control of the primary tumor can usually prevent development of subsequent systemic metastases, tumor radiation fails to control pre-existing systemic disease, which may be present only as micrometastatic (and therefore undetectable) deposits. Combining radiation therapy with immunotherapy allows one to exploit two broad areas: (a) radiation-induced tumor-cell death as a potential source of tumor antigens for immunotherapy, and (b) post-radiation tumor-cell modulation that allows more efficient immune-cell access and increased sensitivity to T-cell killing (*Figure 4*). Preclinical studies and early clinical trials have demonstrated that radiation may enhance the efficacy of therapeutic cancer vaccines, which provided the rationale for current clinical trials employing both modalities combined.

Local irradiation generates an inflammatory microenvironment in which tumor antigens released by dying tumor cells are presented to the immune system in the context of the costimulatory "danger" signals necessary for effective TAA-specific T-cell activation (*Figure 4*).[48–51] In addition, preclinical studies have demonstrated that sublethal doses of radiation induce phenotypic changes in tumor cells, including upregulation of many cell-surface proteins involved in T-cell target recognition, adhesion, and lysis, including ICAM-1, MHC class I and II, Fas, and multiple TAAs (CEA, MUC-1, CA125, Her2-neu, p53, gp70, PSA, PSMA, and PAP). These phenotypic changes render tumor cells more susceptible to T-cell-mediated cytolysis[52–60] and have been specifically shown in mouse models to synergize with DNA, liposome, and poxviral-based vaccine strategies.[50,56,57,59]

Initial clinical data involving a first-generation poxviral vaccine provided clinical proof of concept. Thirty patients with localized prostate cancer were treated with standard radiation therapy, and two-thirds of these patients were randomized to receive vaccine as well. The vaccine utilized in this study was a priming dose of rV-PSA admixed with rV-B7-1, followed by monthly boosts of rF-PSA for a total of eight vaccinations. Thirteen of 19 patients randomized to radiation plus vaccine had a ≥ 3-fold increase in PSA-specific T cells after radiation, compared to no change in T cells in patients treated with radiation alone ($p = 0.0005$).[61] A follow-up study confirmed a similar magnitude of response in a similar proportion of patients.[62]

Samarium-153 (^{153}Sm-EDTMP) is an FDA-approved agent for palliation of bone-related pain in metastatic cancer patients. ^{153}Sm-EDTMP is composed of radioactive samarium and a tetraphosphate chelator that binds to metastatic lesions in bone, targeting low levels of radiation to sites of disease.[63]

In preclinical models, prostate cancer cells exposed to palliative doses of ^{153}Sm-EDTMP upregulated expression of tumor antigens and accessory molecules, rendering tumor cells more susceptible to killing by multiple antigen-specific CTLs (*Figure 4*).[64]

These studies formed the basis for an ongoing randomized phase II study designed to evaluate whether rV/rF-PSA-TRICOM in combination with ^{153}Sm-EDTMP can improve TTP compared to ^{153}Sm-EDTMP alone in patients with CRPC metastatic predominantly to bone. The study will also evaluate the ability of low-level local radiation to generate specific immunologic responses.

Conclusion

Because standard-of-care chemotherapy for mCRPC is associated with only a modest survival advantage and significant toxicity, studies are ongoing to determine if therapeutic cancer vaccines can provide benefit as monotherapy or can synergize with standard therapies, such as radiation or docetaxel. Thus, there is a need for relevant preclinical and early clinical studies to evaluate these approaches. Future clinical trials will also need to incorporate more extensive monitoring of immune responses to help determine how vaccines induce effective tumor immunity, and to validate specific assays that correlate with clinical responses. Finally, nearly all of the clinical trials with therapeutic cancer vaccines have been conducted in cancer patients with advanced-stage disease. The role of these vaccines in the more appropriate patient population with early-stage disease and/or low tumor burden needs to be further explored.

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