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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Current and emerging trends in prostate cancer immunotherapy

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There have been a number of recent developments in the treatment of castration-resistant prostate cancer which seek to exploit the hormonal axis. Still, the castration-resistant prostate cancer remains a major challenge since this is the lethal and incurable phenotype which results in tens of thousands of deaths every year. There has been emerging interest in utilizing anticancer immunotherapy in prostate cancer, especially since the development of sipuleucel-T. Several other prostate cancer therapeutic vaccines including autologous and allogeneic vaccines, as well as viral vector-based vaccines, have demonstrated promising results in early trials. The checkpoint inhibitors which have shown some dramatic results in other cancers are now being studied in advanced prostate cancer setting. Studies are examining the therapeutic effects for both CTLA-4 inhibitors and PD-1/PD-L1 inhibitors. It appears that definitions and measurements of response used in cytotoxic therapies may not be valid in determining response to immunotherapy. Early reports suggest that combination therapies, either concurrent or sequential, may be needed to achieve the desired response against advanced prostate cancer.

The worldwide incidence of newly diagnosed prostate cancers is estimated to be 1.1 million cases, annually. While the majority of patients are initially diagnosed with localized or locally advanced disease, especially in countries where prostate-specific antigen (PSA) screening is widespread, nearly 1/3rd of patients will experience disease recurrence. In countries

where PSA screening is not widely adopted, the incidence of metastatic prostate cancer at diagnosis is significantly higher.¹ While metastatic prostate cancer at initial diagnosis is almost always sensitive to hormonal manipulation, the eventual emergence of castration resistance in this population results in the lethal phenotype termed metastatic castration-resistant prostate cancer (mCRPC). These patients have a median overall survival (OS) between 12 and 36 months.² In the recent years, a number of new drugs have been developed and approved for clinical use in mCRPC patients including cabazitaxel, abiraterone, enzalutamide, and radium-223. These choices remain within the traditional scope of prostate cancer treatment: anti-androgen, chemotherapy, and radiation. While these new therapies have shown survival benefit, a significant proportion of patients will exhibit either primary or acquired resistance to these agents, resulting in a limited clinical response, both in duration and magnitude.³ Clearly, different treatment strategies are needed to improve the survival of men with advanced prostate cancer and mCRPC. Over the last 10 years, research into immunotherapy for the treatment of advanced cancers has led to some promising successes, specifically for melanoma, nonsmall cell lung cancer, and renal cell carcinoma. This has provided the impetus for further investigation into the value of immunotherapy in the treatment of prostate cancer.⁴ Since the development of sipuleucel-T, an autologous cellular immune therapy that stimulates a T-cell immune response against cancer cells, promising clinical trials of immunotherapy for other cancers have stimulated the interest in the development of prostate cancer-specific immunotherapies.

PROSTATE CANCER AND THE IMMUNE SYSTEM

Prostate cancer has several characteristics that make the immune response an important feature in cancer progression and an intriguing target for immune therapy.⁵ A number of different infiltrating immune cells have been detected within prostate cancer tissue, including natural killer cells, CD4+ and CD8+ T-cells, dendritic cells, and tumor-associated macrophages,⁶ all of which can be utilized to unleash host immune responses. The prostate also harbors multiple tumor-specific antigens, such as PSA, prostate acid phosphatase (PAP), and prostate-specific membrane antigen (PSMA), among others,⁷ providing antigenic targets for immune therapy. Furthermore, prostate cancer has slow growth kinetics, which reduces the effectiveness of the traditional chemotherapies but may increase the effectiveness of immunomodulatory approaches, which require time to mount an antitumor response. There is evidence to suggest that, despite the multitude of infiltrating immune cells and tumor-associated antigens, the prostate cancer microenvironment is in fact immunosuppressive in its effect.⁸ It is likely that the immune environment changes over time as the disease status changes and in response to treatment exposure.^{9,10} Manipulation of this inherent immunosuppressive milieu provides another target for therapy. In this article, we will discuss some current and emerging concepts in prostate cancer immunotherapy.

IMMUNOTHERAPY TARGETS

There are two primary immune targeting approaches that seek to exploit the natural immune system to target the cancer cells: (1) antigen-targeted immunotherapy; (2) immunomodulatory immunotherapy. Within these broad categories are several

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more specific targeting concepts: immune checkpoint inhibitors, co-stimulatory antibodies, vaccines, adoptive cell transfer, tumor-infiltrating lymphocytes, oncolytic viruses, and cytokines. The primary focus of current prostate cancer research includes vaccines, which fall into the antigen-targeting group, and immune checkpoint inhibitors and T-cell regulatory drugs, which are classified in the immunomodulatory group.

Autologous vaccine: sipuleucel-T

Sipuleucel-T is an autologous vaccine and a prime example of personalized immunotherapy. It is produced following the collection and processing of patient-derived peripheral dendritic cells (DCs) via leukapheresis. The DCs are then incubated in granulocyte-macrophage-colony-stimulating factor (GM-CSF) and PAP fusion protein (PA2024). After 36–44 h, the primed DCs are re-infused into the patient to generate a PAP-specific CD4+ and CD8+ T-cell response.¹¹ This vaccine was studied in men with early mCRPC who were asymptomatic or minimally symptomatic. The IMPACT trial demonstrated an improvement of 4.1 months in OS compared with placebo, with a 22% reduction in the risk of death. Of note, no difference was noted in time to disease progression or in PSA response.¹¹ The reasons for this are not clear but may be related to the delayed onset of antitumor immune response, an observation which has been repeated in later trials with sipuleucel-T, as well as other cancer immunotherapy trials.¹²

Multiple trials and long-term data have confirmed that this treatment is well tolerated with infrequent and mild adverse events. Since the treatment course is quite short (4 weeks) and side effects are mild, most patients can receive subsequent therapies.¹³ Sipuleucel-T has been used in combination, both as concurrent and subsequent treatment, with other therapies such as abiraterone. This approach appears to have no negative impact on the effectiveness of sipuleucel-T when used in combination with other chemo-hormonal agents.¹⁴ Ongoing clinical trials in this area involve combination studies of chemotherapy, anti-androgens, steroids, radiation, and other immune therapy modalities to further explore their potential for synergistic anticancer effects.

Allogeneic whole cell vaccine: GVAX

GVAX is a GM-CSF tumor cell vaccine. Whole tumor cells (either autologous or allogeneic) can be used as a source of antigen and are modified to express GM-CSF, which facilitates the presentation

of tumor antigens to antigen-presenting cells (APCs), specifically dendritic cells. The maturing dendritic cells stimulate and activate CD8+ T-cells, CD4+ T-cells, and B-cells for the antitumor immune response. The allogeneic GVAX utilizes two human prostate cell lines as the source of antigens, LNCaP (androgen sensitive) and PC3 (androgen insensitive), which are engineered to produce GM-CSF which facilitates recruitment and maturation of APCs near the injection site.¹⁵

Based on promising initial results, a Phase III trial, Vaccine Immunotherapy with Allogeneic Prostate Cancer Cell Lines (VITAL-1), was designed to compare GVAX to docetaxel plus prednisone in asymptomatic mCRPC. A second trial, VITAL-2, was conducted in symptomatic men with mCRPC patients. The VITAL-1 study was terminated early due to a futility analysis showing that <30% of men would reach the primary end point of OS benefit. The VITAL-2 study was also stopped early due to increased mortality rate in the vaccine arm.^{4,16}

Vector-based vaccine: PROSTVAC-VF

PROSTVAC-VF is a recombinant viral vaccine which utilizes PSA as the target antigen. It is based on the combination of two viral particles, including vaccinia, a potent immunologic priming agent, followed by fowlpox, which is used as a boosting agent. Through infection and subsequent lysis of epithelial cells, antigens (e.g., PSA) are released, taken up by APCs, and presented to CD4+ and CD8+ T-cells to mount the desired immune response. To increase the immunogenicity, three co-stimulatory molecules (TRICOM) are incorporated into the vaccine: B7.1, ICAM-1, and LFA-3.^{17,18}

An initial Phase II trial showed that PROSTVAC-VF increased the progression-free survival in 63% of men and significantly lowered the PSA doubling time from 5.3 months to 7.7 months in nonmetastatic prostate cancer.¹⁹ In a different randomized Phase II clinical trial in men with mCRPC, 125 patients with minimally symptomatic mCRPC were randomized to receive the vaccine or placebo. This study did not meet its primary end point of progression-free survival; however, the OS after 3 years was significantly improved (25.1 vs 16.6 months). This apparent discrepancy further supports the paradigm that immunotherapy may be associated with delayed benefits that may continue to develop after completion of treatment.²⁰ The reported side effects have been minimal and are related to injection site reaction

and fatigue or flu-like symptoms. Since this vaccine does not require personalization (as dose sipuleucel-T), the manufacturing and processing of this vaccine is less complex, which may facilitate easier distribution and access for the patients. Based on these encouraging results, a multicenter, international Phase III trial of men with asymptomatic or minimally symptomatic mCRPC for treatment with and without GM-CSF is currently ongoing with completion of patient accrual (NCT01322490).

Other approaches to developing therapeutic vaccines against prostate cancer include DNA-based vaccines, which use a vector, such as plasmid, to encode tumor-associated antigens (e.g., PSA, PAP) to generate an immune response by recruiting APCs.²¹ Another approach involves personalized peptide vaccines, which are developed by first identifying which peptides are most commonly recognized by the precursor cytotoxic T-lymphocytes (CTLs), and then delivery of those peptides results in the activation of CTLs and an antitumor immune response.²² A different autologous-activated DCs vaccine approach has been studied whereby patients' DCs are pulsed with LNCaP cell antigens (DCVAC/PCa). In Phase I/II trials, it was well tolerated with modest antitumor immune response.²³ A Phase III trial of this vaccine in men with mCRPC who are eligible to receive docetaxel is ongoing (NCT02111577). Some of the active and recruiting trials of combining vaccines with other agents for advanced prostate cancer are listed in **Table 1**.

IMMUNE CHECKPOINTS AND T-CELL INTERACTION

The most important and widely studied checkpoint molecules include programmed cell death protein 1 (PD-1) receptor (found on activated/cytotoxic T-cells), programmed cell death ligand 1 and 2 (PD-L1, PDL-2) expressed by tumor cells (advanced or metastatic stage), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). These checkpoints have an inhibitory effect on T-cell function and increase the evasion of tumor cells from the immune system. Thus, inhibiting these immune checkpoints removes their inhibitory effects on T-cells and facilitates antitumor activity by recognition of tumor cells as nonself.

CTLA-4 inhibitors

CD 28 is expressed by T-cells and binds to B7-1 and B7-2 receptors which are present on



Table 1: Currently active and recruiting Phase II and III vaccine trials of and therapy for prostate cancer

NCT number	Phase	Study population	Experimental arms	Investigator	Sponsor
NCT02649439	2	Biochemically recurrent PCa	Prostvac-V/F for 6 months versus surveillance for 6 months then Prostvac-V/F for 6 months	Ravi A Madan, NCI	NCI
NCT02506114	2	Localized PCa	Neoadjuvant therapy prior to radical prostatectomy with Prostvac versus ipilimumab versus Prostvac + ipilimumab	Lawrence Fong, University of California, San Francisco	University of California, San Francisco
NCT02649855	2	Metastatic castrate-sensitive PCa	Standard ADT followed by simultaneous docetaxel + Prostvac versus standard ADT followed by sequential docetaxel + Prostvac versus standard ADT followed by Prostvac, then docetaxel	Ravi A Madan, NCI	NCI
NCT02326805	2	Localized PC, under active surveillance	PROSTVAC-V/F versus placebo	John Parsons, The University of Arizona Medical Center	NCI
NCT02463799	2	Bone metastatic mCRPC	Sipuleucel-T + radium 223 versus sipuleucel-T alone	Emmanuel Antonarakis, Johns Hopkins University	Sidney Kimmel Comprehensive Cancer Center
NCT01804465	2	Chemotherapy-naïve mCRPC	Sipuleucel-T + ipilimumab versus sipuleucel-T + delayed ipilimumab	Lawrence Fong, University of California, San Francisco; Padmanee Sharma, MD Anderson Cancer Center	MD Anderson Cancer Center
NCT01818986	2	mCRPC	Sipuleucel-T + stereotactic ablative body radiation	Raquibul Hannan, University of Texas Southwestern Medical Center	University of Texas Southwestern Medical Center

All trials are from the US government website: www.clinicaltrials.gov. PCa: prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; ADT: androgen deprivation therapy; NCI: National Cancer Institute

tumor cells and APCs to facilitate antitumor effects. CTLA-4 is expressed on activated T-cells and T regulatory cells, and it also competitively binds to B7-1 and B7-2 receptors to block the antitumor immune response.²⁴ Blocking the CTLA-4 T-cell surface protein releases the suppressive effect of the B7 ligands and bypasses the immune checkpoint.

Ipilimumab, a fully human anti-CTLA-4 monoclonal antibody (mAb), was the first checkpoint inhibitor to show clinical activity against melanoma. In a Phase III clinical trial, men with mCRPC with disease progression after docetaxel received ipilimumab and radiation therapy to the bones. This trial did not show an improvement in OS and only demonstrated a modest improvement in progression-free survival. However, in a subset of patients without visceral metastases and favorable laboratory values, a significant improvement in OS was reported (ipilimumab, 22.7 months; control, 15.8 months, HR 0.62; 95% CI: 0.45–0.86; $P = 0.0038$).²⁵ In another Phase III trial, chemotherapy-naïve men with mCRPC were treated with higher doses of ipilimumab. There was no difference in the OS noted, but there was a modest improvement in remission-free survival. This trial failed to confirm the benefits noted in the previous trial in men with favorable disease characteristics that were seen in the previous study.²⁶

To study the immune response mechanism, Gao *et al.*²⁷ treated presurgical prostate cancer patients with ipilimumab and noticed that the treated tumors had scientifically increased activated T-cell infiltration into the tissue but none of these patients had a complete response

to therapy. Through genomic and immune analysis of the resected tumors, they identified higher expression of immunosuppressive molecules, PD-L1 and VISTA, on tumor cells as well as T-cells and other immune cells. These findings lend further support to the idea that tumor cell and immune cell interaction is complex and the immune environment can change as a response to treatment. Based on these findings, the authors have devised a clinical trial to study the role of combination therapy with ipilimumab and nivolumab, and PD-L1 inhibitor to overcome the therapeutic resistance caused by overexpression of inhibitory pathways.

Tremelimumab, another fully human anti-CTLA-4 mAb, has been studied in the setting of recurrent prostate cancer. In a Phase I dose escalation trial, tremelimumab was combined with short-term androgen deprivation therapy (ADT) in patients with biochemically recurrent prostate cancer. Interestingly, while no effect on the PSA level was noted initially, prolongation of the PSA doubling time was noted several months after completing the treatment.²⁸

There are several ongoing trials of CTLA-4 inhibitors with either ADT or with other immune response modulators (Table 2).

PD-1, PD-L1 inhibitors

After infiltrating the tumor environment and recognizing the tumor-associated antigens, the tumor-infiltrating lymphocytes secrete interferon gamma, which promotes the expression of PD-L1 in tumor cells, stromal cells, macrophages, and other white cells. Then, PD-1, which is present on the surface

of T-lymphocytes, interacts with the PD-L1 present in the tumor microenvironment. This inhibits the normal immune response by suppressing the T-cell receptor signaling and giving an anti-apoptotic signal to cancer cells, thus promoting cancer cell survival.²⁹ Another phenomenon, termed T-cell exhaustion, emerges as a result of repeated exposure of T-cells to tumor-associated antigens and sustained PD-1 expression. Sustained PD-1 and PD-L1 expression and interaction result in an immunosuppressive signal to T-cells and an anti-apoptotic signal to tumor cells, which results in the suppression of immune response and prolonged tumor cell survival.³⁰

Several new PD-1 inhibitors (nivolumab, pembrolizumab) and PD-L1 inhibitors (atezolizumab) are under investigation for clinical effectiveness in advanced prostate cancer. These antibodies prevent the interaction between PD-1 and PD-L1 to remove the inhibitory effect. These agents have been approved for clinical use in other cancer types, including melanoma, renal cell, lung, and bladder cancers. Initial clinical trials with these agents and men with mCRPC did not deliver promising results. This may be partially due to the fact that many of these cancers were PD-L1 negative according to immunohistochemical analysis.³¹ Recently reported preliminary results in early trials have been more encouraging. In a Phase IB study with pembrolizumab in men with previously treated advanced PD-L1-positive prostate cancers, stable disease was demonstrated

Table 2: Currently active and recruiting Phase II and III trials of checkpoint inhibitors for prostate cancer

NCT number	Phase	Study population	Experimental arms	Investigator	Sponsor
NCT02788773	2	CRPC	Durvalumab + tremelimumab versus durvalumab alone	Sebastien Hotte, Juravinski Cancer Centre at Hamilton Health Sciences Eric W Winquist, London Regional Cancer Program	Canadian Cancer Trials Group
NCT03204812	2	CRPC	Durvalumab + tremelimumab	Sumit K. Subudhi, MD Anderson Cancer Center	MD Anderson Cancer Center
NCT03093428	2	mCRPC	Radium-223 + pembrolizumab versus radium-223 alone	Lauren C Harshman, Dana Farber Cancer Institute	Dana-Farber Cancer Institute
NCT02787005	2	mCRPC	Cohort 1 - PD-L1 positive with measurable disease: pembrolizumab Cohort 2 - PD-L1 negative with measurable disease: pembrolizumab Cohort 3 - bone metastases with nonmeasurable disease: pembrolizumab Cohort 4 - RECIST 1.1-measurable disease: pembrolizumab+enzalutamide Cohort 5 - bone metastases only or bone-predominant disease: pembrolizumab + enzalutamide	Merck Sharp and Dohme Corp.	Merck Sharp and Dohme Corp.
NCT03007732	2	Hormone-naïve oligometastatic PCa	Pembrolizumab, combined androgen blockade, high-dose brachytherapy versus pembrolizumab, combined androgen blockade, high-dose brachytherapy, and drug SD-101 (TLR9 agonist)	Lawrence Fong, University of California, San Francisco	Lawrence Fong
NCT02312557	2	mCRPC progressing on enzalutamide	Initial treatment phase: patients progressing on enzalutamide receive pembrolizumab Monitoring phase: patients receive enzalutamide after completing pembrolizumab Retreatment phase: patients with disease stability or improvement after initial treatment phase receive pembrolizumab and enzalutamide	Julie Graff, OHSU Knight Cancer Institute	OHSU Knight Cancer Institute
NCT03016312	3	CRPC	Atezolizumab + enzalutamide versus enzalutamide	Hoffmann-La Roche	Hoffmann-La Roche
NCT02985957	2	mCRPC with or without second-generation hormone therapies or taxane-based chemotherapy	Nivolumab + ipilimumab	Bristol-Myers Squibb	Bristol-Myers Squibb
NCT02465060	2	Multitude of cancers, including recurrent prostate cancer, with loss of MLH1 or MSH2 by immunohistochemistry	Nivolumab	Keith Flaherty, ECOG-ACRIN Cancer Research Group	National Cancer Institute
NCT02703623	2	mCRPC	ARN-509 + abiraterone + prednisone versus ARN-509 + abiraterone + prednisone + ipilimumab versus ARN-509 + abiraterone + prednisone + cabazitaxel + carboplatin	Ana M. Aparicio, MD Anderson Cancer Center	MD Anderson Cancer Center

All trials are from the US government website: www.clinicaltrials.gov. CRPC: castration-resistant prostate cancer; PCa: prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; PD-L1: programmed cell death ligand 1

in 39% of men and objective response rate was noted in 13%, lasting for a median 59 weeks. In a Phase II study, pembrolizumab combined with enzalutamide was given to men with mCRPC who had previously failed enzalutamide, and this demonstrated greater than 50% decrease in PSA level, a treatment effect which was sustained for up to 60 weeks in some patients.^{32,33}

At present, there are a large number of ongoing clinical trials to evaluate the role of PD-1 and PD-L1 antibodies in mCRPC and hormone-sensitive prostate cancer, either alone or in combination with other modalities (Table 2).

UNIQUE FEATURES OF CANCER IMMUNOTHERAPY

The beneficial effects of combining immunotherapy with other treatment modalities are being considered in a number of trials, in both hormone-sensitive and castration-resistant prostate cancer. Many therapies have demonstrated potential for benefit but treatment responses have been variable, thus combining different interventions to increase the antitumor response seems desirable. These combinations have included immune checkpoint inhibitors with vaccines, chemotherapy, radiation therapy, focal ablation treatments, surgery, and ADT.⁹

An area of significant interest in the field of anticancer immunotherapy is to identify markers of response to therapy, which includes evaluation of PD-L1 expression on prostate cancer cells. It has been demonstrated in other solid tumors that express PD-L1 show an improved response to anti-PD-L1 therapy. However, the optimum extent of PD-L1 expression, most appropriate technique for measurement, and exactly which tissues to use when testing tumor samples have not been clearly defined for prostate cancer.³⁴ In other tumor types, it has been demonstrated that microsatellite instability and tumor mutational burden (TMB) can predict response to



immune checkpoint inhibitors. In mCRPC, about 6% of tumor samples demonstrated TMB, while 18% of melanoma and 8% of bladder cancer specimens demonstrated TMB. The TMB may be subject to change over the full spectrum of the disease, especially in response to various treatments over time, and ultimately may be an important determinant of therapy response.³⁵

In contradistinction to cytotoxic or androgen suppression therapy, clinical trials in other solid tumors have demonstrated that the best response to immunotherapy was noted in patients with less advanced disease. The PROSTVAC-VF vaccine was shown to be more effective in patients with less aggressive disease.³⁶ Similarly, sipuleucel-T demonstrated improved outcome in patients with earlier disease and less tumor burden.³⁷ This information can help facilitate the identification of the most appropriate patients for studying the effectiveness of immune checkpoint inhibitors.

Other unique and difficult-to-define features of immunotherapy are the timing and duration of therapy and the definition of clinical response. As mentioned above, the maximal clinical response can often be seen months after the end of the treatment. With a number of immune-modulating therapies, such as anti-CTL A-4 antibodies, sipuleucel-T, and PROSTVAC-VF, the response to treatment has been delayed by as much as 6 months, and the peak response has appeared 2–3 years after treatment.^{11,20} Since the OS end point can require additional time and resources, it is a common practice to use surrogate or intermediate end points (e.g., PSA level or progression-free survival) to assess the response to therapy. Recent trials of various immunotherapies including immune checkpoint inhibitors have revealed that an overall survival benefit in favor of the treatment arm can be achieved without measurable effect on the currently used surrogate end points. This has practical implications for clinical trial design, duration of treatment, measuring disease response, and defining a successful outcome.

Immunotherapy has far-reaching potential to treat the full spectrum of prostate cancer ranging from localized disease to mCRPC, but efficacy must first be demonstrated and cost must be addressed. Further work into modifying the tumor microenvironment to be more responsive to a primed immune system will also be important. The future direction of immunotherapy in the treatment of prostate cancer must address several clinical problems, including selecting appropriate patients and

most responsive disease status, determining the dose and duration of therapy, defining clinically relevant outcomes, refinement of combination therapies, and identification of biomarkers of treatment response as well as markers of resistance to immunomodulation. The future of prostate cancer immunotherapy is promising, but there are many obstacles left to overcome.

CONCLUSION

Prostate cancer has several unique features that make it quite suitable for immunotherapeutic approaches. The timing and sequencing of various therapies for prostate cancer requires special consideration. It is apparent that the immune modulation may be best suited for less advanced and slowly progressing cancers. Thus, implementing immunotherapeutic approaches earlier in the prostate cancer disease spectrum would seem to be most appropriate. The standard outcome measures and the assessment of response to therapy used for other therapies are not valid for immunotherapy response measurement. It seems that a combination of immunomodulation approaches such as a vaccine and checkpoint inhibitor or the use of two different checkpoint inhibitors (to counteract the resistance to one agent) would be required to realize the desired antitumor effects.

COMPETING INTERESTS

Both authors declared no competing interests.

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