Convergence of immunotherapy, radiotherapy and prostate cancer: challenges and opportunities

Michael Green¹, Felix Y Feng², Rohit Mehra³ & Daniel E Spratt^{*1}

¹Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

²Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

³Department of Pathology, University of Michigan, Ann Arbor, MI, USA

* Author for correspondence: Tel.: +1 734 647 1372; Fax: +1 734 936 1900; spratt@med.umich.edu

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Immunotherapy has led to unprecedented and durable response rates in multiple cancer types. However, similar success in prostate cancer has not been achieved, leaving patients and the prostate cancer scientific community working harder than ever to understand why and how to identify and select patients who may benefit from these powerful therapies. In parallel, the use of immunotherapy with radiotherapy has demonstrated immense promise in preclinical testing. Given the fundamental role radiotherapy has in the treatment of both primary and metastatic prostate cancer, there is strong rationale for the combination of these two treatments to improve outcomes for prostate cancer patients. Herein, we discuss the state of immunotherapy for prostate cancer and the current obstacles and opportunities available under active investigation.

Prostate cancer is the most common noncutaneous malignancy in men in the USA [1]. However, there remain 26,700 deaths from prostate cancer each year making death from prostate cancer more common than renal cell carcinoma, melanoma and all brain tumors combined each year in men. The primary methods of treatment intensification for metastatic castration-resistant prostate cancer (mCRPC) are intensification of androgen signaling inhibition or addition of cytotoxic chemotherapy. However, few CRPC patients achieve long-term durable control of their disease and ubiquitously succumb to their disease. Thus, there is an unmet clinical need for additional therapies to improve the care of patients with prostate cancer.

Immunotherapy is a true disruptive therapeutic innovation in oncology. Unprecedented response rates, and perhaps more importantly durable response rates, have been achieved in metastatic renal cell carcinoma, melanoma, non-small-cell lung cancer, bladder cancer, Merkel cell carcinoma, lymphoma, among others. However, similarly designed clinical trials in prostate cancer have not demonstrated comparable rates of efficacy leaving patients and the prostate cancer scientific community working harder than ever to understand why and how to identify and select patients who may benefit from these powerful therapies.

In parallel to the surge of positive trials with immunotherapy in other disease sites, the use of immunotherapy with radiotherapy has demonstrated immense promise in primarily preclinical testing. Given the fundamental role radiotherapy has in the treatment of both primary and metastatic prostate cancer for curative intent or palliative benefit, there is strong rationale for the combination of these two treatments to improve outcomes for our patients. Herein, we discuss the state of immunotherapy for prostate cancer and the current obstacles and opportunities available under active investigation.

History of immunotherapy in prostate cancer

Prostate cancer pioneered early immunostimulatory efforts. Sipuleucel-T, which consists of *ex vivo* dendritic cell stimulation with granulocyte-macrophage colony-stimulating factor and the conserved tumor antigen prostatic alkaline phosphatase, was the first US FDA approved cellular immunotherapy in 2010 on the basis of the IMPACT trial [2]. This trial randomized men with minimally symptomatic hormone-resistant metastatic prostate cancer to

placebo or sipuleucel-T. The trial met its primary end point of improved overall survival with a median benefit of 4.1 months, but surprisingly did not induce tumor regression or prevent tumor progression.

More recently, immune checkpoint blockade (ICB) has emerged as a novel therapy capable of producing durable widespread responses across a broad spectrum of malignancies [3,4]. The current FDA-approved agents target CTLA-4 (ipilimumab), or the ligand-receptor conjugate of PD-1 (e.g., nivolumab, pembrolizumab) and PD-L1 (e.g., atezolizumab) to improve adaptive and innate antitumoral immune responses [5]. Unfortunately, randomized control trials examining the role of ipilimumab in the treatment of mCRPC failed to meet their primary end point of improvement in overall survival [6].

Initial Phase I/II studies of nivolumab for a variety of metastatic solid tumors also failed to show a response rate for mCRPC [7]. Preliminary Phase II data have suggested that enzalutamide-resistant prostate cancer patients may have as high as a 30% response rate to pembrolizumab monotherapy, comparable to the rate seen in many other malignancies [8]. While encouraging, this trial has reported on only ten patients to date, and it is unclear if sequencing of therapies or improved patient selection led to the improved response rate for the use of ICB in prostate cancer. Given that there is little to no PD-L1 expression in primary prostate cancer, it is plausible given the increased mutational burden and chromosomal instability of mCRPC that immunotherapy may be more efficacious in this setting. The STARVE-PC trial is examining combination therapy with anti-CTLA4 and anti-PD-1 antibodies in a subset of mCRPC-expressing AR-V7 therapies (NCT02601014), given that this combination has shown to be more efficacious in melanoma therapy as compared with monotherapy.

Biological basis for immunotherapy in prostate cancer

The limited efficacy of immune checkpoint therapy has led to renewed immunological evaluation of prostate cancer. It has been suggested that the low mutational burden of prostate cancer limits the immunogenicity of the tumor [9]. Prostate cancer does, however have many public tissue-associated antigens, including PSA, PMSA, prostatic alkaline phosphatase (the target of sipuleucel-T) and NY-ESO, and there are a variety of Phase I studies examining the potential to target these antigens to elicit an immune response [10]. It is increasingly recognized that tumors undergo a process of adaptive immunoediting which allows the selection and outgrowth of subclones that can grow in an immunocompetent host [11].

Prostate cancer has a long natural history, and autopsy series has shown that even young adult men can have low-grade prostate cancer. This suggests that prostate cancer has a long phase of immune equilibrium during which the immune system can keep the cancer in check [12]. Consistent with this, patients who are placed on chronic immunosuppressive regimens or who develop viral immunosuppression develop a higher rate of solid tumors, including prostate cancer [13]. Further, while tumoral PD-L1 and T-cell PD-1 expression does not ubiquitously serve as a predictive biomarker in response to ICB, multiple studies have shown that prostate cancer expresses PD-L1 and prostate-infiltrating T cells express PD-1 [14,15].

Recently, it has been reported that in enzalutamide-resistant PTEN deleted murine prostate cancer models, the limited efficacy of ICB stems from an immunosuppressive tumor milieu composed of myeloid-derived suppressor cells. Combination of myeloid-derived suppressor cell targeted agents with ICB showed improved tumor elimination, forming the basis for future clinical trials [16]. Finally, other reports have highlighted that ipilimumab and androgen deprivation therapy (ADT) of prostate cancer patients may induce additional immunoinhibitory compensatory mechanisms, including V-domain immunoglobulin (Ig)-containing suppressor of T-cell activation (VISTA) expression [17]. Thus there is a strong biological basis for immunotherapy in the treatment of prostate cancer and several promising leads to potentiate current ICB therapy have been identified.

Radiotherapy & immunotherapy for prostate cancer

Radiotherapy is a noninvasive prostate cancer treatment modality widely utilized both for the definitive management and palliation of painful bony metastases [18]. Radiotherapy induces complex DNA double-strand breaks in tumors, which if not repaired, lead mitotic catastrophe and tumor cell death. On a cellular level, radiotherapy-induced cell death releases danger-associated molecular patterns, such as HMGB1, which induces dendritic cell activation through TLR4 signaling [19]. Further, the DNA damage induced by radiation releases cytoplasmic DNA which elicits Type I interferon signaling and immune activation in a cGAS–STING dependent manner [20].

Preclinically, ionizing radiation has been shown to synergize with ICB by promoting T-cell diversity, improving MHC presentation and inducing abscopal tumor rejection even in nonirradiated lesions [21,22]. Case reports have extended this paradigm to human patients [23]. Despite promising Phase I and II studies, a randomized Phase III

trial of adjuvant ipilimumab following ionizing radiation failed to meet the primary end point of improved overall survival. However, improvements of progression-free survival were seen and there are questions of whether the correct sequence of therapies and dose of radiation were used [24,25].

Hypofractionated radiation schedules that elicit immunologic cell death are also increasingly being utilized for the treatment of definitive prostate cancer [26]. Thus there is a clinical opportunity to examine the role of immunotherapy-based treatment intensification through combination with radiotherapy. However, immunotherapy is associated with serious autoimmune side effects. Institutional studies of prostate cancer patients treated with ipilimumab highlight that CTLA-4 treatments have significant risk of developing grade 3–4 hypopituitarism (18.2%), dermatitis (6.8%) and enterocolitis (15.9%) [27]. Prostate-directed radiotherapy can also cause acute and chronic bowel toxicity [28], and thus treatment intensification will need to be balanced with the potential for increased toxicity profiles.

The interface between hormonal therapy and immunotherapy remains undefined. ADT has been suggested to function by potentiating the DNA damage induced by ionizing radiation, and by reducing the testosterone that fuels prostate cancer growth [29]. Testosterone has long been recognized to contribute to immunologic aging, and castration can lead to improved T-cell number and diversity by limiting thymic involution and contribution to peripheral T-cell homeostasis [30–32]. Murine and human studies have shown that ADT increases T-cell infiltration into the prostate and improves antitumor-associated antigen recognition, suggesting that testosterone may limit host recognition by inducing Ptpn1 and preventing Th1 differentiation [33–36]. ADT has also been shown to potentiate ipilimumab in Phase II trials of prostate cancer [37]. Thus, whether ADT can be exploited to improve immunotherapies remains to be fully assessed.

Conclusion

Despite a series of trials that have not met their primary end point to improve overall survival in prostate cancer, a tremendous amount of knowledge has been gained to potentially help explain the clinical results seen to date. There is a small subset of prostate cancers that harbor a high mutational burden and they should undergo dedicated investigation to determine if comparable response rates can be achieved to other hypermutated tumors [38]. Furthermore, given the low PD-L1 expression of prostate cancer, methods to either increase PD-L1 expression, or investigation, of new therapeutic targets may be necessary. Regardless, immunotherapy continues to hold tremendous promise even for prostate cancer and we anxiously await the results of the many ongoing clinical trials.

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