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Prospects for the future of prostate cancer vaccines

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Abstract

Cancer therapy is undergoing a revolution fueled by clinical data demonstrating that the immune system has significant anti-tumor capability. Although the main focus of this revolution currently rests upon immune checkpoint inhibitors in diseases such as melanoma, lung and bladder cancer, it was actually a therapeutic cancer vaccine in prostate cancer that provided the first data demonstrating that a modern immunotherapy, beyond cytokines, could enhance clinical outcomes. As immunotherapy is poised to take center stage among cancer therapies, the role of cancer vaccines remains somewhat undefined in prostate cancer, though emerging data suggest that vaccines could play a crucial therapeutic role.

Keywords

Vaccines; therapeutic cancer vaccines; prostate cancer; immune combinations; combination therapy

Monotherapy for metastatic disease

Sipuleucel-T was approved in 2010 by the United States Food and Drug Administration for the treatment of minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) based on the results of a phase 3 trial that demonstrated a clinically meaningful and statistically significant improvement in overall survival (OS).[1] Although logistical and financial constraints have somewhat limited its ultimate clinical implementation, the results of multiple phase 3 trials demonstrating an OS benefit provide an important proof of concept that generating an antigen-specific immune response could improve clinical outcomes. Several other vaccines are also being developed as mono-therapy for mCRPC. Prostvac is a pox viral vaccine targeting PSA that has completed accrual in a phase 3 trial (). Other vaccines currently in phase 3 trials in prostate cancer include ProstAtak () and DCVAC ().

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Despite the clinical evidence of efficacy provided by sipuleucel-T as monotherapy in mCRPC, promising pre-clinical and clinical investigations suggest that combination strategies could amplify the therapeutic efficacy of vaccines. There is strong rationale that the use of vaccines earlier in the disease process, in combination with anti-androgen therapies and in conjunction with other immunotherapies, could clinically optimize vaccines for the treatment of prostate cancer.[2]

(Neo)adjuvant vaccines

Although often curable at diagnosis, it is estimated that 90,000 of the more than 220,000 men diagnosed with prostate cancer annually in the United States will have recurrent disease.[3,4] The potential for vaccines to be used in the (neo)adjuvant setting is intriguing. Large tumor burden can be proportionally immunosuppressive, and thus charging the immune system to target small volume, localized disease may amplify the clinical impact in this setting.[5] Pathological findings from the neoadjuvant use of sipuleucel-T suggested that when given in the weeks prior to radical prostatectomy, patients treated with vaccine had increased immune cells at the perimeter of the tumor, perhaps mobilized against the cancer cells.[6] Similar evidence of immune response was also seen in patients with recurrent disease after administration of prostvac [7] and there is a neoadjuvant prostvac study underway (). Can the immune system target micrometastatic sites and “mop up” rogue cancer cells left behind after radical prostatectomy? Certainly, the neoadjuvant sipuleucel-T data suggest that it is possible, although larger clinical trials are required to confirm this hypothesis.

Radiation therapy is another definitive therapy for prostate cancer, and a previous clinical trial has demonstrated that a vaccine can enhance the immune response in patients treated with radiation.[8] In addition to killing individual cancer cells in an immune-stimulatory manner, radiation can also increase immune recognition (as demonstrated by increased antigen and MHC expression) and immune cytolitic activity (via up-regulated molecules such as Fas).[9] Each of these attributes provides a strong rationale to combine vaccines with definitive radiation therapy and invoke a form of the abscopal effect on distant sites of disease.

Previous trials in the neoadjuvant setting have primarily focused on immunologic or pathologic endpoints, but if the neoadjuvant strategy is to become more consequential, trials with clinical endpoints will be required.

Combination studies with anti-androgens

Anti-androgen therapies are integral to treating recurrent or metastatic prostate cancer. In addition to this critical role, anti-androgen therapies have demonstrated their ability to generate an immune response. Androgen suppression has been shown to enhance naïve T-cell production from the thymus.[10] Recent preclinical studies have suggested that the androgen receptor antagonist enzalutamide has similar effects. [11] Additional studies have suggested that androgen suppression can decrease immune tolerance, thereby increasing immune recognition of prostate cancer cells.[12] Also, neoadjuvant androgen deprivation

therapy (ADT) studies have demonstrated increased T-cell trafficking to the prostate.[13] The immunologic properties of anti-androgen therapy support the potential therapeutic benefit of immune combinations with ADT or drugs such as enzalutamide.

The importance of this is highlighted by the growing understanding of treatment resistance in prostate cancer. Recent studies have indicated that sequential use of anti-androgens such as abiraterone and enzalutamide results in overlapping mechanisms of resistance (androgen receptor (AR) splice variants (ARVs)). [14] Clinical data also suggest that the efficacy of docetaxel is limited after therapy with these newer anti-androgens, suggesting additional, common escape pathways.[15] Since a vaccine-initiated anti-tumor response likely impacts the disease via immune recognition beyond the AR pathway, it is unlikely that ARVs or other similar resistance mechanisms will curtail this immunologic effect. In fact, translocations or truncations could lead to neo-epitopes that may be immunogenic. Thus, while anti-androgens could potentiate a greater vaccine-initiated immune response, the concomitant use of vaccines and anti-androgens could enable a longer clinical response by inducing a disparate immunologic attack in addition to the AR-targeted activity of anti-androgens. Multiple vaccine studies are underway in combination with anti-androgens (, and).

Immune combinations: vaccines to potentiate immune checkpoint inhibitors

Perhaps the most provocative recent development with vaccines is their potential role when used in combination with immune checkpoint inhibitors. Monoclonal antibodies targeting PD1 and PDL1 have recently demonstrated impressive clinical efficacy in patients, but that benefit is limited to patients whose tumors seem to express high levels of PDL1. Preliminary data from studies in melanoma, head and neck, lung and bladder cancer all suggest that response rates to anti-PDL1/PD1 therapy are substantially increased in patients who have biopsy-proven PDL1 expression.[16] For example, in head and neck tumors, response rates have been reported as high as 46% in PDL1-positive patients but only 11% in patients whose biopsies stain negative. Even in melanoma, which has seen some of the greatest benefits thus far from anti-PD1 inhibition, the discrepancy of response among patients with PDL1-positive tumors and PDL1-negative tumors has been as high as 49% vs. 13%. Similar findings have been reported in bladder cancer (43% vs. 11%) and lung cancer (46% vs. 15%). Ultimately, these data suggest that even in cancers where PD1/PDL1 inhibition has been most effective, approximately 80% of patients are not likely to have PDL1-positive tumors, thereby limiting potential benefit.

PDL1 expression, however, may be a surrogate marker for a pre-existing, underlying immune response. PDL1 expression is not static such as estrogen receptor status in breast cancer, rather it is typically dynamically expressed such as when the tumor encounters immune cells in the tumor microenvironment. Preclinical data indicate that PDL1 expression can be induced after increasing exposure of the tumor to IFN-γ, a cytokine produced by activated T cells.[17] Based on these findings, the potential for success of PD1/PDL1 checkpoint inhibitors is likely greatest in patients who have already developed some degree

of anti-tumor immune response. The next step in this therapeutic revolution is to induce an anti-tumor immune response in the majority of patients who have PDL1-negative tumors.

Therapeutic cancer vaccines may be one approach to induce an anti-tumor immune response, enhance PDL1 expression and thus broaden the efficacy of PD1/PDL1 inhibition. This may be especially important in prostate cancer where PDL1 expression has been reported to be quite low (>10%).[18] Therapeutic cancer vaccines would be administered to patients to activate T cells in the periphery, which would potentially migrate to the tumor as suggested by earlier studies.[6,7] Once in the tumor microenvironment, these activated T cells would produce IFN-γ, thereby inducing PDL1 expression on the tumor, as has been modeled preclinically. [17] These same studies have demonstrated increased anti-tumor effect when anti-PDL1 molecules are then combined with vaccines.

A second strategy could employ vaccines with immune checkpoint inhibitors such as anti-CTLA-4. Unlike anti-PD1/PDL1, anti-CTLA-4 treatments are more likely to work in the periphery (as opposed to the tumor microenvironment) to enhance and sustain T-cell activation. Early studies with multiple vaccines in prostate cancer have demonstrated relative safety and potential efficacy.[19,20] Future studies could combine vaccines with antibodies targeting anti-CTLA-4 and PD1/PDL1 to optimize this immune intensification strategy.

Conclusion

The immunotherapy revolution in cancer is underway, but the greatest results may be yet to come, and therapeutic cancer vaccines may be a vital component. This may be especially true in prostate cancer, where one vaccine is approved and several others are in the final stages of clinical testing. Combinations with anti-androgen therapies could enhance the efficacy of the primary therapy for recurrent or metastatic disease. Using vaccines to enhance PDL1 expression and potentiate the efficacy of anti-PD1/PDL1 therapies could also have a significant clinical impact in a disease where baseline PDL1 expression, which may reflect underlying immune response, is reportedly low. Ultimately, vaccines added to definitive therapy, perhaps with anti-androgens and/or PD1/PDL1 inhibition, could be used in the (neo)adjuvant setting to enhance the cure rate of clinically localized disease at high risk for recurrence. We are only beginning to understand the antineoplastic capability of the immune system, and it seems likely that vaccines will be crucial in unleashing its true potential.

Biographies

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