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RESEARCH HIGHLIGHT

Combining active immunotherapy with immune checkpoint blockade for the treatment of advanced prostate cancer

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Combination immunotherapy is emerging as a promising approach for the treatment of advanced prostate cancer. This research highlight discusses the combination of a PSA-directed poxviral vaccine and a monoclonal antibody blocking an important immune checkpoint molecule to treat men with metastatic castration-resistant prostate cancer. The results demonstrate feasibility and safety, as well as intriguing clinical responses to this combination therapy.

Although prostate cancer has not traditionally been considered a disease amenable to immune-directed therapy, this notion has recently been challenged with the Food and Drug Administration (FDA) approval of sipuleucel-T for the treatment of men with advanced prostate cancer. This approval came on the heels of a pivotal phase III trial investigating the autologous cellular immunotherapy product, sipuleucel-T, which showed an improvement in survival relative to placebo among men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.[1] However, treatment with sipuleucel-T does not usually produce declines in prostate-specific antigen (PSA) levels, nor does it commonly induce tumor regressions in metastatic lesions. Therefore, investigations are underway to attempt to further augment anti-tumor immune responses in prostate cancer patients by combining therapeutic vaccines with other immune-modulating agents. One strategy has focused on the use of drugs that inhibit immunological checkpoint molecules: proteins that are expressed on T lymphocytes that serve to attenuate overexuberant immune responses. One such approach involves the use of a monoclonal antibody blocking cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), a negative regulatory molecule expressed on the surface of T cells. To this end, ipilimumab has shown encouraging clinical activity in patients with advanced melanoma, where it has been associated with an improvement in overall survival,[2,3] leading to its FDA approval in that disease.

In a recent issue of *Lancet Oncology*, Madan and colleagues[4] explored the combination of a therapeutic prostate cancer vaccine given in conjunction with a CTLA-4 blocking antibody in men with metastatic castration-resistant prostate cancer. The specific vaccine used in this phase I study was PSA-Tricom, a poxviral-based immunotherapy that contains transgenes expressing PSA, as well as three T-cell costimulatory proteins. This vaccine was recently shown to improve survival compared to placebo in an unplanned secondary analysis of a randomized phase II trial in men with advanced prostate cancer.[5] In the present study, 30 patients with docetaxel-refractory or chemotherapy-naive metastatic castration-resistant prostate cancer were treated with a fixed dose of the PSA-Tricom vaccine (administered subcutaneously at study entry, and at monthly intervals thereafter) in combination with escalating doses of ipilimumab (1, 3, 5 or 10 mg kg^{-1}, given intravenously at monthly intervals). The top-line results were that this combination was feasible and tolerable, with an acceptable safety profile. Most adverse events were immune-related, and included vaccination site reactions, colitis, rash, aminotransferase elevations and endocrine effects (hypothyroidism, adrenal insufficiency and hypophysitis). Several clinical responses were seen, as measured by PSA declines after treatment initiation. Fifty percent of patients (15/30) experienced some reduction in PSA, while 20% (6/30) achieved PSA declines of 50% or more. In addition, median survival in the overall patient cohort was 34 months, which is somewhat longer than expected in this patient population.

How do these safety and efficacy data compare with those when each agent is used alone? Previous studies have shown that PSA-Tricom is associated with very minimal toxicity, manifesting primarily as mild injection site reactions, low-grade fever, chills, fatigue and nausea. However, only about 1% of patients receiving PSA-Tricom achieved a $\geqslant$50% reduction in PSA.[5] On the other hand, adverse events with ipilimumab are more common and often more serious than those associated with PSA-Tricom, and include immune-related toxicities such as rash, colitis, hepatitis, and endocrine-related dysfunction (grade 3–4 immune events occur in about 23% of treated patients).[2] It should be remembered that because the physiologic role of CTLA-4 is to attenuate autoimmune phenomena, treatment with ipilimumab may induce a number of breakthrough autoimmune events. In contrast to PSA-Tricom and other therapeutic vaccines (where PSA responses are infrequent), single-agent ipilimumab is capable of inducing PSA reductions of 50% or more in about 15% of patients with metastatic castration-resistant prostate cancer.[6] In the combination study reported by Madan and colleagues,[4] grade 3–4 immune-related toxicities were observed in 27% of patients (8/30), which might suggest that this class of adverse events could be slightly intensified when ipilimumab is coadministered with PSA-Tricom. However, alternative explanations for the apparent marginal

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increase in toxicity may relate to the older patient population (median age 69 in the Madan study,[4] and 56 in the melanoma study[2]), as well as possible higher scrutiny in adverse event documentation in the setting of a phase I (rather than a phase III) study. In addition, the majority of immune-related events in the Madan trial were managed successfully by discontinuing ipilimumab, administering systemic corticosteroids, and replacing hormones (e.g., levo-thyroxine) where appropriate. Finally, PSA response rates appeared to be enhanced with the combination of PSA-Tricom and ipilimumab, especially in men who had not received prior chemotherapy (in whom $\geqslant$50% PSA reductions were seen in 25% of cases).

The current study is important, because it provides a proof of principle that administration of immune checkpoint blockade in combination with therapeutic cancer vaccines may enhance anti-tumor immune responses, ultimately improving patient outcomes. Indeed, other recent clinical studies have also explored the notion of combining active immunotherapies with immune checkpoint inhibitors. For example, a similar phase I trial which was also conducted in patients with metastatic castration-resistant prostate cancer combined ipilimumab with an allogeneic whole tumor cell vaccine.[7] In that study, PSA responses of $\geqslant$50% were observed in 25% of men, while immune-related adverse events were also observed frequently. These studies may also provide the rationale to combine active cancer vaccines with monoclonal antibodies targeting PD-1, another immune checkpoint molecule whose inhibition might be associated with fewer immune-related toxicities than ipilimumab.[8] Finally, there is mounting preclinical evidence that prostate cancer immunotherapy may be enhanced by combining it with standard hormonal therapies as well as novel androgen-directed approaches, and several clinical trials are currently underway to test this hypothesis.[9] Future progress in the treatment of prostate cancer will likely depend on rational combinations of immune-directed agents with conventional prostate cancer treatments, in an attempt to ultimately improve outcomes of patients with this disease.

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