Therapeutic vaccines for prostate cancer: what have we learned?

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'Preclinical studies and now clinical trials suggest that, when testing a therapeutic vaccine as a single modality, patients with more indolent and less advanced disease are more likely to have better immune responses and increased overall survival.'

Several characteristics of prostate cancer make it an attractive target for immunotherapy. The majority of tumors are relatively indolent, allowing for sufficient time to generate an immune response prior to disease progression. In addition, given the relatively few cytotoxic therapies of proven benefit, a large number of patients with advanced prostate cancer have had limited or no prior chemotherapy that can decrease the ability to mount an immune response.

In recent years, numerous preclinical and clinical studies have investigated a variety of approaches to prostate cancer immunotherapy, including the use of vaccines consisting of whole tumor cells, antigen-presenting cells (APCs) and poxvirus-based vaccines. These trials are not only providing initial evidence of clinical efficacy, they are highlighting the importance of end points and patient selection in clinical trial design. This editorial reviews a few promising vaccines for prostate cancer and how clinical trials of these agents alone inform us about immunotherapy clinical trial design for metastatic castrate-resistant prostate cancer (CRPC).

Whole tumor-cell vaccines

Whole tumor-cell vaccines use irradiated prostate cancer cells to generate an immune response. The majority of trials have been conducted with allogeneic vaccines, which are produced from established, readily available prostate cancer cell lines that can be manufactured on a large scale. GVAX (Cell Genesys, South San Francisco, CA, USA), a granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting vaccine, is an admixture of prostate cancer cell lines PC-3 and LNCaP. In two separate multicenter Phase II trials, patients with asymptomatic CRPC given high-dose GVAX had a median survival of 26.2 to 35.0 months [1]. By estimating predicted survival based on a commonly used nomogram [2], patients in both trials exceeded anticipated survival by more than 6 months. Based on these data, Cell Genesys has launched two Phase III trials in patients with metastatic CRPC. The trials, both of which have overall survival as their primary end point, are comparing docetaxel and prednisone versus GVAX or docetaxel and prednisone versus docetaxel plus GVAX.

Another promising whole tumor-cell vaccine, Ony-P1, demonstrated early encouraging prostate-specific antigen (PSA) kinetics changes and time to metastatic disease data in a single arm Phase II trial [3]. An ongoing multicenter placebo-controlled Phase IIb trial is evaluating time to metastatic disease in patients with nonmetastatic CRPC.

Antigen-presenting cell vaccines

Dendritic cells (DCs) are highly proficient APCs that localize to many sites, including epithelium in the skin, gut, lung and genitourinary tract. DCs are a valuable component of vaccine therapy, as they express both class I and class II major histocompatibility complexes (MHC), and thus are able to stimulate a wide range of lymphocytes.

Sipuleucel-T (Dendreon, Seattle, WA, USA) consists of an autologous APC-enriched product pulsed with a recombinant fusion protein-containing prostatic acid phosphatase (PAP; expressed on over 95% of prostate cancer cells) and GM-CSF. In Phase I and II trials, a significant number of patients receiving sipuleucel-T had PSA declines of 25–50% [4,5]. Patients who developed an immune response to PAP also had a longer median time to progression [4].

In a recently completed Phase III trial of sipuleucel-T [4], there was a trend to improved time to progression in patients treated with vaccine versus placebo ($p = 0.054$). Moreover, there was statistically significant improvement in overall survival with vaccine (25.9 versus 21.4 months; $p = 0.01$). However, as overall survival was a secondary end point in this trial, a confirmatory Phase III study with overall survival as the primary end point is currently under way.

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Poxvirus-based vaccines

Immunization with live recombinant poxviral vaccines induces expression of tumor-associated antigens (TAAs) and other transgenes engineered into the vectors, allowing antigen processing by DCs and other APCs for T-cell activation. The interaction of T-cell receptors with MHC and TAAs triggers the initial immune response. However, a second costimulatory signal is needed to generate a potent T-cell response through the release of cytokines. A triad of costimulatory molecules (B7.1, ICAM-1 and LFA-3) called TRICOM has been engineered into poxviruses.

In a Phase II study using PSA-TRICOM for patients with metastatic CRPC (n = 32), three patients had PSA declines of 30 to greater than 50%. One of 12 evaluable patients had a partial response by Response Evaluation Criteria in Solid Tumors criteria and three patients had radiographically stable or improving disease after 12 months or more on study. There was also a strong correlation between clinical benefit and an increase in PSA-specific T cells following vaccine.

A company-sponsored multicenter randomized Phase II study in 125 patients with metastatic CRPC (Gleason score ≤7) did not meet its primary end point of progression-free survival [6,7]. Patients' overall survival data are currently being accumulated, with provocative results. Median overall survival thus far is 16.3 months for the control cohort (wild-type vector) (n = 41) versus 24.4 months for those patients receiving PSA-TRICOM vaccines (n = 84).

Patient selection

Preclinical data suggest that therapeutic vaccines are most likely to be effective in patients with less aggressive tumors and lower tumor burden [8]. Recently, Halabi *et al.* have identified criteria associated with overall survival in metastatic CRPC [2]. These seven criteria are related to aggressiveness of disease (Gleason score) or disease burden (visceral disease, performance status and baseline lactate dehydrogenase [LDH], alkaline phosphatase, PSA and hemoglobin). By using these parameters in a nomogram, overall survival can be predicted.

In the company-sponsored PSA-TRICOM study, patients were stratified by bisphosphonate usage, with 43% of patients on bisphosphonates in both arms. Virtually the entire apparent survival advantage of vaccine-treated patients versus those treated with control vector was seen among patients who were not on bisphosphonates, probably because they had less advanced disease. These patients had lower median PSA, LDH and alkaline phosphatase and higher median hemoglobin than patients receiving bisphosphonates, all of which are independent predictors of survival [2]. Indeed, all patients had Gleason ≥ 7 tumors, favorable performance status and no visceral metastasis, making the other Halabi parameters the only variable ones.

Similarly, in the sipuleucel-T trial, patients had relatively good baseline characteristics (no visceral disease, ECOG 0–1) and their median PSA, LDH, alkaline phosphatase and hemoglobin reflected a relatively good prognosis. The only presented Halabi score parameter used to group patients in this trial was Gleason score. Interestingly, although there were improvements among vaccinated patients in all subgroups, differences in both survival and time to progression were substantially larger in the Gleason ≤7 subgroup. In addition, early data suggested that immune responses were significantly improved in this subset [10].

Concerns over labeling limitations may tempt industry trialists to include all patients with CRPC. However, preclinical studies and now clinical trials suggest that when testing a therapeutic vaccine as a single modality, patients with more indolent and less advanced disease are more likely to have better immune responses and increased overall survival, which translates to smaller, more cost-effective trials. Conversely, patients with more aggressive and advanced disease are more likely to derive benefit from vaccine if used in combination therapy.

Clinical end points

We have previously addressed the issue of end points for vaccine studies [7]. Objective evaluation of disease response is difficult in metastatic CRPC. Approximately 60% of patients with metastatic CRPC have metastasis only to bone, visualized best by whole-body scintigraphy. Unfortunately, complete responses with whole-body scintigraphy are rare, and there are no widely accepted criteria for partial responses. Furthermore, increasing radionuclide uptake is associated with bone healing (possibly a therapeutic response), trauma and progressive disease, further complicating interpretation. Only approximately 40% of patients have measurable soft tissue disease (largely lymph node metastasis). In immunotherapy trials, waxing/waning lymph nodes may represent vaccine-driven therapeutic changes.

In addition, there is emerging evidence suggesting that patients treated with vaccine may have better responses to subsequent therapies than patients who do not receive vaccine [7,11]. This is best exemplified by the sipuleucel-T trial in which patients who went on to receive docetaxel at progression were followed. Despite the groups being well balanced in terms of baseline characteristics, there was a striking and statistically significant increase in overall survival (HR 1.9; p = 0.023) with docetaxel treatment in patients who had prior vaccine (34.5 months, n = 51) versus placebo (25.4 months, n = 31) [12]. This may result from subsequent therapy causing destruction or decreased function of regulatory elements within the immune system (e.g., regulatory T cells), apoptosis of tumor cells in a way that stimulates the immune system, a decrease in immune regulatory substances elaborated by tumor cells and alteration of tumor-cell phenotype that makes tumor cells more amenable to immune-mediated recognition and destruction. These factors (difficulty with radiographic studies and possibility of improving future therapies) may explain why both the sipuleucel-T and PSA-TRICOM studies (approximately 120 patients each) failed to meet a time-to-progression end point, yet showed apparent overall survival benefit. Thus, overall survival is the preferred end point of definitive vaccine clinical trials in metastatic CRPC.

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Conclusion

Sophisticated vaccine therapies have been developed, some of which are showing improved clinical outcomes, including survival benefit, without significant toxicity. If early survival data are replicated in larger trials, it is likely that a vaccine will be approved for prostate cancer within 2–3 years. However, it is imperative that such registration trials be designed using appropriate patient selection methods and clinical end points.

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