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EDITORIAL OVERVIEW

A year of successful cancer vaccines points to a path forward

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Results from recent clinical trials of the therapeutic vaccines sipuleucel-T (Dendreon Corp), PROSTVAC-VF-TRICOM (National Cancer Institute/BN ImmunoTherapeutics Inc) and BiovaxID (Biovest International Inc) are highlighted. These data support the further development of such vaccines, and provide guidance for the development of improved agents and protocols for the use of therapeutic vaccination to treat cancer.

Introduction

Enthusiasm for cancer vaccines has fluctuated during previous years, as initial indicators of success were subsequently countered by failures. Nonetheless, new opportunities may arise as a result of data from unsuccessful clinical trials that have provided new information on how the immune response is modulated in patients with cancer. During 2009, positive data from several vaccine trials have been reported, and these successes may provide useful hints that are applicable to the development of the next generation of cancer vaccines.

Sipuleucel-T

The phase III, randomized, double-blind, placebo-controlled, IMPACT (IMmunotherapy for Prostate AdenoCarcinoma Treatment) clinical trial assessed the autologous APC-based vaccine sipuleucel-T (PROVENGE; Dendreon Corp) for the treatment of men (n = 512) with asymptomatic or minimally symptomatic, metastatic, androgen-independent prostate cancer; the trial achieved the primary endpoint of improving overall survival [1]. Sipuleucel-T is generated by a process in which autologous PBMCs obtained from patients by leukapheresis are cultured with a recombinant fusion protein containing GM-CSF and the prostate tumor-antigen prostatic acid phosphatase. Compared with placebo, sipuleucel-T extended median survival (21.7 versus 25.8 months, respectively), improved the 3-year survival rate by 38% (23.0 versus 31.7%, respectively), and reduced the risk of death by 22.5% (hazard ratio [HR] = 0.775). However, sipuleucel-T did not delay time to progression (TTP) significantly, a clinical endpoint which, until relatively recently, had been accepted as the gold standard. The results from the IMPACT trial were consistent with those from two previous trials with this vaccine [2], as well as with results from another recent phase IIb trial using allogeneic tumor cells [3] that also failed to meet the TTP endpoint. TTP is a difficult endpoint to measure in prostate cancer because of the difficulty in measuring non-bony metastases, but vaccines may increase overall survival without initially preventing tumor growth. One mechanism by which overall survival could be increased despite no increase in TTP would be if the biological activity of the vaccines was directed toward micro-metastatic disease rather than toward bulk tumors. In this case, an immunological approach (as used in vaccine strategies) would become efficacious only once the cancer begins to spread. In addition, the prolonged period of time required for the patient to develop an adequate immune response with a vaccine may result in the continuation of tumor progression at early time points following immunization, although after the immune response has become adequate (which may occur after a patient has transitioned to another anticancer therapy), progression of the disease may be slowed sufficiently to affect survival. If this delayed effect is determined to be common with therapeutic vaccines such as sipuleucel-T, then a paradigm shift is required in the study of such vaccines – using overall survival as the primary endpoint may be necessary. In addition, further exploration of potential surrogate markers of survival (including identifying immune markers that correlate with survival) will be required to guide the development of new generations of vaccines. Moreover, the collection of data regarding the time period following disease progression from patients who participate in vaccine trials may become necessary also.

The experience gained with sipuleucel-T provided several useful insights. First, prostate cancer may be an appropriate target for cancer vaccines despite the prostate being viewed historically as an immunologically privileged site, because of the relatively low levels of MHC expression that occur in that tissue. Second, the slow growth rate of prostate cancer allows adequate time for a sufficient immune response to the vaccine to develop and have an impact on the ultimate outcome of disease; the lack of TTP benefit may reflect the growth of the tumor before the onset of metastatic disease, a phase during which the stimulated immune response is sufficiently potent to control progression. Third, a clinical trial comparing the vaccine with placebo may be more appropriate than comparing the vaccine with an active chemotherapy, which acts more rapidly and often exhibits immunosuppressive effects. Fourth, the APC approach (eg, as used in the sipuleucel-T vaccine) may be a potent vaccine platform; for example, CD54 expression by APCs may correlate with improved outcome [4]. Fifth, the autologous vaccine approach by definition requires patient-specific production of the vaccine and, therefore, may be best regarded as a process available only to a select group of patients who have access to the necessary equipment and expertise. Whether or not immunotherapy should proceed along such a 'personalized' route in the future will require further evaluation, but this approach is considerably more complex than 'off-the-shelf' agents.

PROSTVAC-VF-TRICOM

In a successful phase II clinical trial, PROSTVAC-VF-TRICOM (PV; National Cancer Institute/BN ImmunoTherapeutics Inc), a prime-boost vaccine regimen consisting of two recombinant viral vectors (vaccinia and fowlpox), each encoding transgenes for PSA and for a combination of three costimulatory molecules (B7.1, ICAM-1 and LFA-3; so-called TRICOM), was investigated in patients with non-aggressive metastatic prostate cancer who had increasing PSA levels despite castrate testosterone levels and a Gleason score of < 7. Patients in this trial were randomized (2:1) to receive either PV (vaccinia prime plus six doses of the fowlpox boost) plus GM-CSF or placebo, which consisted of empty vector plus control saline injections [5]. Similar to the sipuleucel-T trial, patients who received PV demonstrated a longer median survival compared with patients who received the placebo (24.5 versus 16 months, respectively; HR = 0.6; 95% confidence interval = 0.4 to 0.9; stratified log rank p = 0.016). However, progression-free survival (PFS) was not increased in the PV group.

Based on the data obtained in the PV clinical trial, prostate cancer can be regarded as an appropriate target for cancer vaccines, and the use of either viral vectors or a prime-boost strategy is supported; however, a previous trial of PANVAC-VF (National Cancer Institute), a vaccinia- and fowlpox-based vaccine that encodes CEA and MUC-1 in addition to TRICOM, was unsuccessful in patients with pancreatic cancer, suggesting that not all tumors are responsive to a prime-boost strategy. The observation of survival benefit without a concomitant PFS benefit suggests that, as with sipuleucel-T, trials should use overall survival as the primary endpoint. PANVAC-VF is administered with GM-CSF, which is part of the fusion molecule used in the production of sipuleucel-T, to cause APC migration to the immunization site. However, a trial of GM-CSF in combination with melanoma peptides reported no benefit of the combination compared with peptide vaccinations in the absence of GM-CSF [6]; therefore, the role of GM-CSF remains to be clarified.

BiovaxID

A third vaccine for which promising data were reported in 2009 was BiovaxID (Biovest International Inc) [7], a patient-specific, autologous tumor-derived idiotype (Id)-based vaccine that was investigated in a phase III, randomized, double-blind, placebo-controlled clinical trial in patients with previously untreated advanced follicular lymphoma. BiovaxID is generated by fusing lymphoma cells obtained by lymph-node biopsy with a myeloma cell line to create a heterohybridoma. The secreted idiotype is then affinity-purified and conjugated to keyhole limpet hemocyanin (KLH). Notably, only patients who achieved a complete response, or an unconfirmed complete response following chemotherapy progressed to the second stage of the trial, in which patients were randomized (2:1) to receive either vaccination with Id conjugated to KLH plus GM-CSF (BiovaxID) or a control (KLH plus GM-CSF). Only a small fraction of the intended population of patients was enrolled in this trial, and the number of patients who were immunized with BiovaxID was smaller than intended. However, at a median follow-up of 56.6 months (range = 12.6 to 89.3 months), the median time to relapse following treatment with BiovaxID was 44.2 months, compared with 30.6 months for patients in the control arm (HR = 1.6; p = 0.045). Although this trial has been criticized for the incomplete patient accrual and failure to meet the predefined statistical significance level of $p < 0.01$, the data suggest that the hybridoma-derived Id vaccine exhibits clinical activity.

Despite the negative results obtained from two previous clinical trials of Id-based immunizations, namely mitumprotimut-T (FavId) and GTOP-99 (MyVAX) [8,9], the improvement in the time to relapse observed in the most recent trial with BiovaxID may indicate that the particular approach used to generate the Id may be important. For example, mitumprotimut-T and GTOP-99 were produced by proprietary recombinant technologies, and there were differences in the constant region of the Id-containing immunoglobulin and the glycosylation patterns of the resulting Ids. Moreover, patients may need to exhibit a complete response in order to benefit from a vaccine; two of the negative Id vaccine trials included patients who had not achieved a complete response.

Conclusion

In summary, positive clinical trial data with cancer vaccines suggest that progress in the development of therapeutic vaccines may be achieved with several

different vaccine platforms, although all three of the vaccines discussed in this editorial overview involved the use of either GM-CSF to recruit dendritic cells or dendritic cells themselves in the vaccine construct. A relatively unexplored issue has been whether the more efficient delivery of antigen to dendritic cells at the injection site would correlate with improved immune responses and clinical outcomes. Therapeutic vaccines may be successful against indolent tumors or minimal residual disease only. The established metrics for assessing clinical activity need to be reconsidered for cancer vaccines. Moreover, none of the clinical trials discussed in this overview examined the role of immune regulatory or suppressive mediators, such as regulatory T-cells (Tregs) or myeloid-derived suppressor cells; greater activity might be observed if treatment strategies combined immunization with inhibitors of these cells. For example, the use of GM-CSF or high-dose IL-2, as reported in a recent phase II trial of a peptide-based vaccination against melanoma [10], may provide the immunological impetus necessary to overcome Treg activity and to initiate a successful antitumor response. Interestingly, interim data from a phase III trial of a chimeric anti-GD2 antibody for the treatment of neuroblastoma suggested that this antibody was effective only when combined with GM-CSF and IL-2 [11]. Cancer vaccines have a positive future, but the design of trials assessing such vaccines will be critical in order to provide data that are useful to guide progress, rather than to merely confirm previous inconclusive results. In conclusion, the solutions proposed by the 2008 Biotherapy Development Association are particularly appropriate: "better patient selection, use of multi-modal treatments that affect several aspects of the immune system at once, a requirement for the development of good biomarkers to stratify patients for selection prior to trial and as surrogates for clinical response, and harmonization of SOPs [standard operating procedures] for immunological monitoring of clinical trials" [12].

Suggested reading

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