Developing effective cancer vaccines

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Introduction

Induction of vaccine-induced immune responses against tumour antigens is hampered by an immunosuppressive environment in cancer patients and by effective tolerisation of the immune system against self-antigens. As a result only modest clinical efficacy has been recorded from clinical trials utilising cancer vaccines. However, despite these disappointing results, recent findings from clinical studies have shown that new paradigms of vaccination schedules may well lead to cancer vaccines with improved clinical efficacy.

Vaccine formulation

There is consensus that optimally designed cancer vaccine trials combining the most effective carriers with the right antigens might yield positive clinical results. Dendritic cells (DCs) are the most potent antigen-presenting cells in the body and therefore there is great interest in their use as vaccines for cancer immunotherapy. DC-based vaccine constructs are adapted to present antigens or a complex of antigens including peptides, proteins, cell lysates, DNA and RNA. Sipuleucel-T (Provenge) is a vaccine consisting of patients' DCs loaded with a fusion protein linking GM-CSF to prostatic acid phosphatase, before intravenous administration. A phase III clinical study, IMPACT, has met its primary endpoint by improving the OS of asymptomatic or minimally symptomatic castrate-resistant prostate cancer patients vaccinated with Sipuleucel-T by 4.1 months compared with placebo (25.8 months versus 21.7 months) [1]. US Food and Drug Administration (FDA) approval was granted in April 2010, making Sipuleucel-T the first therapeutic cancer vaccine approved for cancer treatment. Viral vectors expressing tumour antigen plus costimulatory molecules also represent efficacious vaccine formulations. PSA-TRICOM (PROSTVAC) is a recombinant pox viral vector expressing a slightly modified PSA transgene along with B7.1, ICAM-1, and LFA3 costimulatory molecules. Vaccinated prostate cancer patients had a greater 3-year overall survival (OS) compared with the placebo arm (30% versus 17%) and an improvement in median OS of 8.5 months (24.5 months versus 16 months) [2].

The requirement of $CD4^+$ T cells helps to increase the efficiency of induction and the establishment of long-term $CD8^+$ T cell immunity is well established and for this reason, $CD4^+$ T-helper peptides have been included in vaccine preparations. A novel method of increasing the potency of helper peptide vaccines has been the use of the invariant protein (Ii-Key). Specifically, the addition of a four-amino-acid sequence (LRMK) to T-helper peptides facilitates direct (no intracellular processing) epitope loading of MHC class II molecules at the cell surface, thus significantly increasing antigen presentation compared with the unmodified class II epitope *in vitro*. Studies from our laboratory and from others have shown AE37, the Ii-Key hybrid of HER-2/*neu*(776–790) to be highly efficient in generating both *in vitro* and *in vivo* antitumor immunity [3]. Based on these data, AE37 has entered in two phase I (breast and prostate cancer) studies where it proved to be safe and immunogenic [4,5]. A breast cancer phase II study is now ongoing. A mix of long peptides from the HPV-16 viral oncoproteins E6 and E7 encompassing a variety of CTL and helper epitopes induced 30% complete responses that lasted for more than 2 years in women with vulvar intraepithelial neoplasia. These responses were correlated with HPV-16-induced immunity [6].

Stage of disease

Tumours at early-stage disease are more amenable to treatment (less antigenic heterogeneity, more likely to express MHC, less immunosuppressive). In the adjuvant setting, 53 women with node-positive breast cancer were vaccinated with a HER-2/*neu* vaccine (E75) plus GM-CSF. The vaccine was well tolerated and all vaccinated patients demonstrated E75-specific $CD8^+$ T cells. At 20 months' follow-up, the recurrence rate was 5.6% for the vaccinated group compared with 14.2% in the control group [3]. In a multicentre phase III clinical trial, 254 patients with stage II

and III colon cancer were randomly assigned, after curative resection of a primary tumour, to receive OncoVAX (Vaccinogen; a vaccine composed of irradiated autologous tumour cells) treatment [7]. The 5.8-year median follow-up showed a 20.4% reduction in risk of disease progression in patients receiving OncoVAX compared with the control group. Analysis by stage showed no significant benefit of OncoVAX in stage III disease, whereas a statistically significant improvement in recurrence-free survival (RFS) in stage II was reported, with a 41.4% reduction in relative risk of disease progression in the OncoVAX arm.

Duration of treatment and follow-up

In a phase III study, Oncophage (Vitespen; an autologous tumour-derived HSP gp96 peptide complex vaccine) was compared with the physician's choice (PC) of treatment for stage IV melanoma [8]. Patients were randomly assigned 2:1 to receive Oncophage (25 μg weekly for the first four vaccinations and then every other week) or PC. Results from this trial suggested a survival benefit of patients with M1a or M1b disease who were able to receive vaccinations for an extended period of time. Moreover, RFS curves in these groups of patients diverged at almost 1.5 years' follow-up. Similar results were also observed from another phase III study with renal cell carcinoma patients post-nephrectomy at stage I or stage II disease [9]. Trials in advanced-stage settings efficacy outcomes can be assessed quickly in rather small samples of patients. In contrast, trials in the adjuvant setting involve patients with earlier disease stages and better prognosis for whom conventional therapies can occasionally be curative. Given that active immunotherapy, in contrast to chemotherapy, does not act directly on cancers, but stimulates the immune system to act on the cancer, trials in the adjuvant setting require increased duration of vaccination period as well as a long assessment period to obtain sufficient efficacy data.

Conclusion

There are several parameters including vaccine design, the clinical setting in which vaccines are used and duration of treatment and follow-up, that when carefully formulated may lead to improved clinical efficacy. However, given the complexity of interactions between tumours with the immune system as well as the suppressive milieu induced by the developing tumours, therapeutic vaccination should be combined with other modalities. There is now evidence to suggest that chemotherapy combined with vaccination therapy might provide substantial clinical benefits. In addition, biological therapy in the form of small molecule inhibitors (e.g. tyrosine kinase inhibitors) may subvert key tolerising tumour-induced conditions, making cancer vaccines more efficacious. Such combinatorial therapies in cancer are expected to induce improved clinical responses.

Conflict of interest statement

The authors declare no conflict of interest.

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