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RESEARCH HIGHLIGHT

The delivery of effective therapeutic cancer vaccination

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The recent *New England Journal of Medicine* article[1] describing the Phase 3 placebo controlled trial (Immunotherapy for Prostate Andenocarcinoma Treatment) was much anticipated. Its publication and peer review brings down the curtain on the, at times controversial, application by Dendreon to the US Food and Drug Administration. The Immunotherapy for Prostate Andenocarcinoma Treatment data lead to the US Food and Drug Administration's final approval in April of the product sipuleucel-T (Provenge) as the first therapeutic vaccine for use in individuals with asymptomatic or minimally symptomatic hormone refractory metastatic prostate cancer. The prospect of harnessing the immune system to treat prostate[2] and other cancers is alluring and these events provide a much needed boost to the concept. Patients, oncologists and scientists now see therapeutic vaccination as an important, low side effect, option to add to the growing list of new anticancer drugs.

The innate (immediately reactive) and cognate (memory and specific) immune system has, by definition, failed in the cancer patient but it appears to protect us from very early cancers. The complex immune interactions between patients and their cancers are being unraveled and the immunological tools to intervene are emerging.[3] Dendritic cells (DCs) are unique types of white blood cells, which act as antigen presenting cells (APCs), i.e. they monitor the host and present exogenous (pathogens, transplants) and host (normal tissue and abnormal cancer) antigens to the other cellular components, thereby discriminating between friend and foe. These instructions dictate the strength and character of the immune response. However, the growth of the cancer and its use of 'every evasion tactic, just like viruses' often overwhelms any immune response. In prostate cancer, the failure to activate DC[4] and the inappropriate downregulation by regulatory T cells[5] results in a minimal or no-anticancer cytotoxic T lymphocyte (CTL) or antibody response. Therapeutic APC or DC vaccination removes the patient's cells from the *in vivo* suppressive milieu, loads them with cancer targets and after activation returns them to the patient with the aim of boosting any incipient immune response.

To make sipuleucel-T, APCs (including DCs) are prepared from density gradient separated mononuclear cells and incubated with recombinant fusion protein (PA2024), consisting of prostate acid phosphatase and granulocyte–macrophage colony-stimulating factor. The former provides the target and the latter activates the APC. The multicentre, double blinded, placebo-controlled trial assigned 512 patients in a 2 : 1 ratio to receive either sipuleucel-T or placebo (cells not exposed to PA2024) intravenously for three infusions at two weekly intervals. The primary endpoint was overall survival (analysed by a stratified Cox regression model adjusted for baseline levels of serum prostate-specific antigen and lactate dehydrogenase). There was a relative reduction of 22% in the risk of death in the sipuleucel-T group compared with the placebo group (hazard ratio, 0.78; 95% confidence interval, 0.61–0.98; $P=0.03$). This represented a 4.1-month improvement in median survival (25.8 months versus 21.7 months). The time to objective disease progression was similar in the two study groups, a feature of an earlier trial.[6] After objective disease progression most (109/171) control patients received a frozen version of sipuleucel-T at the physician's discretion and they had an extended mean survival of 23.8 months compared to 11.6 months for the untreated control subgroup. There was evidence of immune recognition in the sipuleucel-T treated patients: 28.5% had antibody titres to prostate acid phosphatase>400 (this subgroup lived significantly longer) and 15/55 tested had a T-cell proliferative response. The analysis of adverse events provided reassuring data in terms of autoimmune events (a major theoretical concern) and features common to such protocols namely chills, fever and headache.

The isolation and *ex vivo* loading of APCs for therapeutic vaccination joins the *ex vivo* expansion of CTLs[7] as an established cellular therapy. The use of circulating blood cells (with preformed DCs) rather than the more widely used monocyte-derived DCs, which were unsuccessful in Phase 3 melanoma studies, and the use of granulocyte–macrophage colony-stimulating factor activation may have been important. Improvements to the process may involve testing purified (antibody selected) DC preparations, individual DC subsets and other activators such as toll receptor ligands. Viral, DNA and peptide vaccines are also being trialed in prostate cancer[2] and it is also encouraging that a poxviral prostate-specific antigen vaccine prolonged survival in a randomized Phase 2 study.[8]

Which prostate antigens to target is an issue. Only one target antigen (prostate acid phosphatase) was used in the Immunotherapy for Prostate Andenocarcinoma Treatment study. An effective immune response can broaden the targets engaged but using more target antigens upfront should add weight to the initial low frequency CTL response. An increasing number of novel prostate target antigens are under evaluation. Any prostate-specific antigen might be used for immunological ablation and this makes for a much less restrictive therapeutic immunological index (the increased antigen expression and CTL availability for malignant as opposed to normal tissues) than applies in other cancers. It may take an extended course of active vaccination before an adequate CTL response occurs and longer courses will need to be studied in time.

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The application of immune therapies is expected to be most effective in early disease or when initial treatment (surgery radiotherapy or chemotherapy) has achieved a minimal residual disease state and the patient's immune system is able to respond. Recent data have shown that DC vaccination of patients with acute myeloid leukemia in conventional remission but with molecular minimal residual disease can eradicate the leukemia marker.[9] DC vaccination therapy may also be combined effectively with surgery or radiotherapy and certain conventional cytotoxic drugs, including docetaxel. There is also an opportunity to combine it with other immune therapies, e.g. passive antibody therapies and passive infusions of expanded CTLs and/or depletion or blockade of regulatory T cells. To cure, immune strategies will need to target the prostate cancer stem cell[10] or its supporting cellular environment.

At practical level, the perseverance of many investigators in cancer immunotherapy is beginning to pay off. The emergence of commercially driven models for cellular and other biological therapies will enhance its progress.

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