Cancer vaccines – hope or hype?

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There have been many false dawns in the field of cancer vaccines, but some of the new products look distinctly promising.

Using vaccines that stimulate the immune system to fight cancer appeals to many as a natural approach that is both safe and effective. And, judging from a recent headline in the UK newspaper *The Times* – "Vaccine jab could cure lung cancer" – there is clear public interest in this area. Even big pharma is showing signs of excitement. At a partnering conference one of the more traditional majors said cancer vaccines had moved from the 'no strategic interest' category to 'watchful waiting' – an almost seismic shift to those of us who remember past scepticism. But is there promise beyond the hype? And can vaccines find a place in modern cancer therapy?

The immune system has always played an important role in cancer prevention. Pre-malignancies, induced by toxic chemicals, excessive exposure to UV radiation, viral infection or simply spontaneous genetic mutations, arise at intervals throughout the body. They are generally detected and destroyed by a panoply of immune mechanisms, mostly before we are aware that anything untoward has happened. On rare occasions, this occurs after the clinical manifestation of cancer, resulting in spontaneous regressions. Vaccine treatment aims to harness these mechanisms in a therapeutic setting.

The prospect of avoiding the severe side-effects associated with many treatments underpins the demand for cancer vaccines. Despite recurrent vaccine hysteria, safety, selectivity and potency remain the hallmarks of a vaccine, and cancer vaccines promise efficacy with limited – or no – side-effects. Serious adverse events have been the exception in the clinical trials of experimental vaccines conducted to date. At the same time, there have been few glimpses of real benefit, with numerous false dawns and much disappointment.

But there was an explosion of interest in this field after the unravelling of mechanisms for triggering cytotoxic T-cell (CTL) response about 15 years ago. It was a fundamental breakthrough in immunology that provided insights into the workings of the immune system and how to activate and direct it to attack cancers. Moreover, our knowledge of how cancers, in turn, deploy defence mechanisms to evade or disable the immune system has also increased.

Cancer vaccines can be divided into three categories. The first group, non-specific immunostimulants, covers the agents BCG, interleukin-2 and interferon alpha, which are used to treat bladder cancer, renal cell carcinoma and malignant melanoma. They boost levels of activity in the immune system to reverse immunosuppression induced by the tumour, resulting in rejection of the cancer. Although many agents have been tested, few have been successful and these failures have tarnished the entire field.

Specific-target vaccines are based on the antigens expressed by tumours but not by normal tissues. There are numerous variants: subunit and anti-idiotype vaccines and immuno-gene therapy to name but three. Much effort has been directed toward high-tech solutions in this area, but it has become apparent that tumours continue to mutate as the disease progresses, evading the immune system by downregulating or losing the expression of the target antigen.

The third group, multivalent and ultravalent vaccines, combine several antigens in one formulation to overcome immunological evasion. This is akin to combination chemotherapies, whereby resistance to one element is mitigated by the presence of others. Taking this concept still further, a number of vaccines use inactivated whole cancer cells because they contain the entire spectrum of tumour antigens in an ultravalent formulation.

Cell vaccines

The most encouraging results so far have come from cell vaccines. These have moved the state of the art beyond safety and immunogenicity into the realm of clear clinical benefit. Indeed, in 70 recently published vaccine trials, half used cell therapies (late-stage clinical highlights are shown in the box).

Broadly speaking, there are two types of cell vaccine: patient-tailored (autologous) and off-the-shelf (allogeneic). The autologous approach involves harvesting patients' tumour and immune cells, processing them ex vivo to induce immuno-

logical activity and then returning them to the donor. Companies using autologous tumour cells include German firm LipoNova, California-based Cell Genesys, Avax Technologies from Kansas and Intracel from Maryland.

From a scientific standpoint, autologous cell vaccines have significant merit, matching the tumour antigens precisely to the patient being treated. They have also produced favourable results in trials of several cancers. But interest in this approach has waned because of inherent logistical difficulties and the associated high costs.

The other autologous technology employs patients' immune cells. Dendreon, IDM from Paris, France, Merix from North Carolina and Geron, based in California, use dendritic cells (DCs), whereas Xcyte and Targeted Genetics, both of Seattle, Washington, use T-cells. Again, this approach is scientifically and medically sound, but doubts remain as to whether the treatments can be applied across broad patient populations.

Allogeneic cell vaccines rely on the cancer antigens present in a high percentage of tumour types. Although the spectrum of tumour-specific and tumour-associated antigens (TSAs and TAAs respectively) will be unique to a tumour deposit, some cell lines express tens if not hundreds of common antigens at high frequency. When immortalised, these cell lines can be used in vaccines. They grow indefinitely in culture systems and can be manufactured at industrial scale in modern cGMP facilities.

Another advantage of allogeneic cell vaccines is that the concept behind them – they are a product in a bottle rather than a bespoke service – is familiar to the pharma industry. Furthermore, the costs are lower from economies of scale and, importantly, they are readily available (there are no lengthy lead times as there may be with certain autologous systems).

The leading proponent of this approach is Dr Donald Morton, founder of CancerVax and a pioneer in clinical cancer immunotherapy for more than four decades. CancerVax's lead product, Canvaxin, is composed of three human melanoma cell lines rendered replication-incompetent through irradiation, with BCG used as a vaccine adjuvant for the initial two doses. Canvaxin, which is currently in two international randomised Phase III trials in malignant melanoma, has arguably produced better safety and clinical efficacy data than those supporting the approval of several new cancer therapies.

Other companies active in this area include Cell Genesys (which also has autologous-vaccine programmes) and London-based Onyvax, whose lead product for prostate cancer, Onyvax-P, is in Phase II trials, data from which will be reported later this year.

Next steps

The field of cancer vaccines has matured considerably over the past few years. Several products are in Phase III trials with the prospect of potential product registrations over the next 18 to 24 months. If all goes to plan, vaccines could be available to patients in 2006 or 2007.

Although significant challenges and risks remain – as they will until the first cancer vaccine is registered – these have shifted away from the early proof-of-concept issues towards the practical realities of manufacturing and regulatory affairs.

This, together with compelling data from late-stage trials, is convincing the sector that cancer vaccines represent much more than hype.

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RECENT TRIAL RESULTS

RCC Vaccine (LipoNova). The renal-cell carcinoma vaccine was tested in a 55-centre, 558-patient trial. At 70 months, progression-free survival rates were 72% in the vaccine group and 59.3% in the control group. The product was well tolerated, with only 12 adverse events associated with the treatment.

Canvaxin (CancerVax). In a sample of 263 patients who underwent complete resection of clinically detectable stage IV melanoma, 150 people received post-surgical treatment with Canvaxin in Phase II protocols and 113 received other or no adjuvant therapy. Median overall survival and five-year overall survival were significantly increased in patients who received the treatment vaccine compared with those who didn't (36 compared with 18 months, and 39% compared with 19%).

Provenge (Dendreon). In a randomised Phase II/III trial in hormone refractory prostate cancer, patients receiving Provenge had a significant survival advantage, with an 89% average overall increase in survival time compared with the placebo group. Median survival time in the treatment group was 30.1 months compared with 22.3 months among people who were not treated. At 30 months from randomisation, the survival rate for Provenge-treated patients was 3.7 times higher than for those receiving placebo.

This article was first published in Scrip Magazine, May 2004 (134, 6-7). Reproduced by permission of PJB Publications Ltd.