Cancer vaccines edge towards success

Richard Harrop* and Stuart Naylor*

A number of cancer vaccines are now entering the final stage of clinical development. Are vaccines finally on their way to enjoying mainstream success in the oncology arena?

Over the past decade, vaccination strategies for the treatment of cancer have been investigated with renewed vigour, perhaps catalysed by a greater understanding of tumour immunology and the clinical successes achieved with monoclonal antibody and cytokine-based therapies. However, before vaccines become fully integrated into the arsenal of weapons currently used to treat cancer, they must show not only efficacy but also safety and limited or no toxicity. Recently, a number of cancer vaccines have moved into the stages of development where clinical benefits and good safety profiles can be determined convincingly.

Reports from a number of Phase II and Phase III studies suggest cancer vaccines are not only well-tolerated but that they are also meeting clinical endpoints, ranging from significant tumour responses to improvements in median survival time. Results from such trials build on a significant body of Phase I clinical data which suggest that, in general, this class of therapeutic is safe and that the attributed adverse event rate is low. Cancer vaccines that have such a safety profile may be readily integrated into current standard-of-care regimens, particularly in the first-line setting where combination strategies prevail over monotherapies.

Targeted vs non-specific

Cancer immunotherapies can broadly be divided into two categories: tumour-specific and highly-targeted products, for example vaccines or antibodies that target a specific tumour antigen, and therapies which modulate the immune system in a non-tumour-specific way. An example of the latter is BCG, which has been used for many years in the treatment of bladder cancer and has been shown to provide superior benefits over chemotherapy regimens in patients with a high risk of progression. While the precise mode of action of the treatment is not known, it is accepted that it has an effect on the immune system.

Likewise, the cytokines IL-2 (interleukin 2) and IFNa (interferon α) have found widespread use in the treatment of different malignancies, such as renal cancer and melanoma, yet they offer only modest benefits and frequently lead to toxic side-effects.

In between these two approaches lie cell-based therapies, in which whole tumour cells or cell extracts are used as the immunogen. While tumour-specific immune responses may be induced, the precise target(s) of the response is not usually known. Furthermore, immune responses against other common tissue antigens may also be induced. Despite the lack of fine specificity of the immune response induced and the labour involved in the production of autologous, cell-based therapies, a number of products have completed Phase II and Phase III trials with promising results.

The explosion in the identification of tumour-associated antigens (TAAs) in multiple cancer types which occurred in the 1990s represented a critical phase in the ability to apply tumour immunology research to the development of immunotherapy strategies. This discovery enabled the development of targeted treatments and allayed some of the safety concerns over the deleterious autoimmune

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A number of studies suggest cancer vaccines are not only well-tolerated but meet clinical endpoints

reactions that can result from less specific approaches. The successful targeting of specific tumour antigens in vivo has been exemplified by the use of monoclonal antibodies. Although they failed to live up to their promise in the 1980s, they have since enjoyed a renaissance in the treatment of different cancers, and there are currently eight therapeutic antibodies approved by the Food and Drug Administration (FDA) for sale in the US. Campath (alemtuzumab), Rituxan (rituximab), Herceptin (trastuzumab), Mylotarg (gemtuzumab ozogamicin), Zevalin (ibritumomab tiuxetan), Bexxar (tositumomab), Erbitux (cetuximab) and Avastin (bevacizumab) achieved total sales in excess of US$3 billion in 2004.

While the success of monoclonal

antibody therapies cannot be denied, other targeted approaches are now waiting in the wings, including vaccination. Unlike monoclonal antibodies, which are usually delivered as a bolus infusion, a vaccine's therapeutic potential has to be transduced through multiple biological steps within each patient before any clinical benefit is realised. This offers both advantages and disadvantages over the more direct effects of infused monoclonal antibody therapies. On the positive side, a vaccine-based approach:

- Induces a broad polyclonal cellular and humoral immune response
- Leads to a response of potentially greater longevity, requiring fewer injections
- Does not require 'humanisation' of the immune response, unlike the use of monoclonal antibody therapies, which are usually of murine origin
- Costs less

However, success is dependent on the induction of a potent and 'appropriate' immune response in a patient group that may be immuno-compromised. Furthermore, an efficacious response may take a month or more to induce. Despite these drawbacks, a diverse array of cancer vaccines has made the transition from pre-clinical research to clinical development over the past 5–10 years. The positive results now being observed in the clinic owe much to a greater understanding of the immune system, the timing and method used to deliver the therapeutic antigen(s) and the increased sensitivity of monitoring tools.

The main contenders

Given the time and money required to take a product from pre-clinical research to pivotal Phase III clinical trials, only a small number of cancer vaccines have to date progressed to the stage at which efficacy can be established convincingly. However, clinical responses including tumour shrinkage, disease stabilisation and improvements in time-to-disease progression are being reported in controlled trials. And more importantly, statistically significant increases in patient survival have been detected (see Table).

For example, in June 2004, Aphton Corporation of Philadelphia announced the results of a Phase III trial of Insegia, a synthetic peptide, similar to a portion of the hormone Gastrin 17, linked to the diphtheria toxin. The study compared Insegia with placebo in patients with advanced pancreatic cancer and demonstrated a statistically significant increase in patient survival time; 150 days for patients receiving the vaccine compared to 83 days for those on placebo.

And in February 2005, Seattle-based Dendreon announced encouraging results for its immunotherapy product Provenge – autologous dendritic cells loaded ex vivo with a recombinant fusion protein consisting of the TAA prostatic acid phosphatase linked to GM-CSF (granulocyte/macrophage colony-stimulating factor). It was reported that treatment with Provenge significantly improved survival in men with asymptomatic, metastatic androgen-independent (hormone-refractory) prostate cancer when compared to placebo. According to the final three-year intent-to-treat analysis of the randomised Phase III study, patients receiving Dendreon's investigational product showed a 4.5-month improvement in median survival time and a more than three-fold increase in survival after 36 months compared to patients receiving placebo. This is now being followed up with a second Phase III clinical trial, with the objective of confirming recent findings so that FDA approval of Provenge may be sought.

Other immunotherapies have led to positive results in subsets of treated patients, for example, antibody responders in Aphton's Phase II trial of Insegia in colorectal cancer patients, or in multiple, open-label Phase II studies including CancerVax' trials of Canvaxin in melanoma. In the latter study, retrospective analyses showed treatment with Canvaxin, which consists of irradiated cancer cell lines, significantly improved survival of patients with stage IV melanoma. The median overall survival time of 268 patients with the cancer, who received Canvaxin following the surgical removal of their tumours, was 42.4 months compared to 14.3 months for 170 historical control patients who did not receive the vaccine.

Furthermore, a Phase IIb study of Canadian firm Biomira's BLP25 liposome vaccine, a synthetic MUC1 peptide encapsulated in a liposome delivery system, has shown encouraging improvements in overall survival in non-small-cell lung cancer (NSCLC) patients – although it did not quite attain statistical significance – and it has been granted fast-track approval by the FDA.

Another candidate is TroVax, a vaccine based on the TAA 5T4 delivered by the attenuated vaccinia virus, MVA (modified vaccinia Ankara), under investigation by Oxford BioMedica in the UK.

A recent announcement reported interim data from two Phase II clinical trials in which TroVax was administered in combination with chemotherapy to patients with late-stage colorectal cancer.

Immune responses specific to antigen 5T4 were observed in 100%

of patients who were suitable for analysis. This observation is particularly encouraging given that a retrospective statistical analysis of data collated from a Phase I/II study showed a highly significant correlation between the strength of 5T4-specific immune responses and time-to-disease progression.

The following immunotherapies are also in late-stage clinical development: Oncophage from Antigenics in New York, PANVAC-VF from Therion Biologics in Cambridge, Massachusetts, and TG4010 (MVA-MUC1-IL2) from Transgene in Strasbourg, France.

Tempered expectations

Cancer vaccine strategies are often at odds with classical clinical development approaches. For example, they are usually trialled in potentially refractory patient groups in which the ability to galvanise an immune response may well be compromised. And the decision as to where a cancer vaccine is best placed as a therapeutic is a difficult one. Scientifically, the adjuvant setting, in which disease burden is minimal, may well represent the optimal slot to detect clinical benefits. However, it requires a bold decision to commit to this type of study, because large patient numbers are required and clinical endpoints are protracted. Financially, this translates to trials that are exceptionally expensive to conduct and that take many years to yield results, and this is problematic, especially for biotech companies. The selection of both indication and setting, whether adjuvant, first-line or second-line treatment, has to balance the speed in reaching clinical endpoints with the time needed for the immune response to become effective in 'disease management'.

The expectation that vaccines will cure cancer may have to be tempered in certain indications and settings. While tumour regressions have been observed in a number of clinical trials, stabilisation of disease leading to enhanced survival may be a more realistic expectation in patients with large tumour burdens or with rapidly growing cancers.

Despite the challenges, this is an exciting time for the cancer vaccine investigational arena. Results from some of the Phase III trials, such as studies on Canvaxin, GVAX and PANVAC-VF should be available this year or early 2006.

If the primary objectives are met, product registration could follow within a year or two.

Furthermore, important advances are being made in the search for surrogate markers and the ability to predict whether individual patients are likely to respond to a specific treatment. Such information will help to refine the design of clinical trial protocols and target patients who are more likely to gain benefit from the immunotherapy. Subsequently, it is hoped that cancer vaccines will soon become commonplace alongside surgery, chemotherapy and radiotherapy for the treatment and management of cancer.

SELECTED CANCER VACCINES IN LATE-STAGE CLINICAL DEVELOPMENT

Company	Product name	Indication	Trial stage	Trial status	Survival benefit
Antigenics	Oncophage	Renal	Phase III	Part I closed	Not yet available
Aphton	Insegia (G17DT)	Pancreatic[1]	Phase III	Completed	Increase in overall survival[2]
		Pancreatic	Phase III	Completed	Yes (statistically significant)
		Colorectal	Phase II	Completed	Increase in overall survival[2]
Biomira	Theratope	Breast	Phase III	Completed	None
	BLP25	NSCLC	Phase IIb	Completed	Yes (but not statistically significant)
CancerVax	Canvaxin	Melanoma	Phase III	Closed	Not yet available[3]
Cell Genesys	GVAX	Prostate	Phase III	Active	Not yet available
Dendreon	Provenge	Prostate	Phase III	Completed	Yes (statistically significant)
Onyvax	Onyvax-P	Prostate	Phase II	Closed	Not yet available
Oxford BioMedica	TroVax	Colorectal	Phase II	Closed	Not yet available
		Renal	Phase II	Active	Not yet available
Therion Biologics	PANVAC-VF	Pancreas	Phase III	Active	Not yet available
Transgene	TG4010	NSCLC	Phase II	Active	Not yet available

NSCLC – non-small-cell lung cancer [1]With/without chemotherapy [2]In antibody-positive patients [3]Encouraging open-label Phase II studies

Green is the new black

Edzard Ernst*

It enhances survival in ovarian and prostate cancer patients and protects their hearts against damage from chemotherapy drugs. Could green tea be a new wonder drug?

IN Japan, 5.5 billion bottles of green tea were consumed last year. Yet in Europe, green tea is drunk by few. Which is a pity, because it is probably the healthiest choice. Like black tea, green tea is made from the leaves of the tea plant *Camellia sinensis*. The difference is essentially that, for black tea, the leaves are fermented, while for green tea they are not. Green tea therefore contains plenty more chemicals called polyphenols. These are powerful antioxidants with exotic names, such as catechins, epicatechin, catechins gallate and epigallocatechin gallate. It is these ingredients that may make green tea good for our health.

Years ago, epidemiologists noted that cancer rates in populations that consume green tea were lower than expected. We should not get too excited about such findings. For instance, tea drinkers could also be avoiding things that cause cancer or have a lifestyle that protects them. But encouraging results about green tea kept coming in and eventually formed a compelling body of evidence. The curiosity snowballed and, currently, research into the health aspects of green tea is buoyant.

Studies in test tubes show that the ingredients of green tea inhibit tumour growth and cause the death of cancer cells. In animal experiments, green tea impedes the development of chemically induced cancers. Some green tea ingredients seem to enhance the effect of anticancer drugs. Other compounds protect our organs against the damage that cancer drugs can have, for instance, on the heart. Taken alongside chemotherapy, green tea could maximise the benefits of such drugs and minimise their risks.

These effects may be valuable for a range of cancers. Importantly, they are supported not just by one or two investigations, but by dozens of studies from around the world.

But the proof of the pudding is in the eating.

Do we have data from clinical trials, or is all this based on lab experiments? So far few such studies have been completed. A rare exception is a prospective investigation from China of 254 women with ovarian cancer. While 78% of the green tea drinkers survived for longer than three years, the figure was only 48% for the abstainers. The authors of this study therefore believe that "increasing the consumption of green tea ... may enhance epithelial ovarian cancer survival." Another analysis found similar effects for sufferers of prostate cancer.

Antioxidants in green tea are not only important for cancer, they might also play a role in cardiovascular disease. Regular green tea consumption normalises lipid metabolism, reduces blood pressure, slightly lowers body weight, stabilises glucose metabolism in diabetes patients, and might even neutralise some effects of smoking. Collectively these effects are likely to amount to a significant protection from heart disease, stroke and other cardiovascular problems.

However, clinical trials are again scarce. A Japanese team observed 203 patients who underwent a coronary angioplasty. Of these, 109 had coronary artery disease while the rest had normal coronaries. Patients with normal coronary arteries consumed significantly more green tea compared to those who had diseased

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In a Chinese study, 78% of green tea drinkers, but only 48% of abstainers, were alive at three years

coronary arteries. The authors were optimistic: "The more green tea patients consume, the less likely they are to have coronary artery disease." Before you rush out to buy a car load of green tea, a word of caution. All these findings are encouraging but, to be sure, we really need the results of clinical trials. These will take a while to come through. The good news is that green tea is delicious and refreshing. The bad news is that to match the dose used in the research studies, you need to drink up to 12 cups a day.