Recent progress in immunotherapy: anti-cancer vaccines, emerging clinical data

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the history of cancer vaccines

The history of cancer vaccines has been reviewed in great detail previously and only the salient points will be made here. Many reviewers state that the scientific concept of vaccines really started with Coley’s toxins at the turn of the twentieth century. However, he was trying to replicate the fever and ‘cytokine storm’ that he had witnessed following sepsicaemia when he observed the regression of some tumors. The acute febrile state he was trying to induce would not exactly be regarded as a cancer vaccine approach by today’s standards. Although there are some remarkable tumor responses recorded using non-antigen-specific approaches, such as Bacille Calmette–Guerin (BCG) and other mycobacteria, especially when given intratumorally, the majority of cancer vaccines in development today are very much focused on targeting specific tumor antigens. The first of these approaches was to use autologous tissue as the best source of antigens. Establishing a cell line from the patient’s own tissue was regarded as one of the best sources of antigens but it is far from practical, with many patients failing to produce a cell line. Nevertheless, the only two published trials showing clinical benefit for a cancer vaccine in a randomized study are for colorectal and renal cell cancer [1, 2]. Interestingly, the approach was not successful for melanoma, where many of the vaccine studies are targeted, as by the time a cell line was established, many of the patients would have progressed and died. To overcome this unreliable reproduction, several investigators began to use allogeneic cell lines with shared antigens to the tumor. The allogeneic cell lines could be injected either as whole-cell vaccines after irradiation or used as lysates. The most researched of all these approaches was the triple allogeneic cell vaccine developed by Donald Morton and his colleagues at the John Wayne Cancer Institute [3, 4]. Although very impressive clinical results in a single institute, with historical controls correlating with very specific immune responses were accumulated over decades, a randomized study in multiple centers throughout the world failed to establish a significant survival difference over patients treated with a placebo vaccine, which incidentally included BCG as the initial adjuvant [5].

This is only one of several vaccine approaches targeted at melanoma which have had very good phase II single institution data but failed to meet major endpoints when used in multicentre randomized studies [6]. Apart from the several obvious reasons to explain phase III failures (such as the product being ineffective or the selection of inappropriate populations for investigation and the need to identify patients likely to respond to vaccine), the fact that melanoma may be a poor choice of tumor due to its proclivity to rapidly double in size and metastasize in a totally unpredictable manner may be the most important reason of all.

Nevertheless, melanoma has remained the training ground for a number of different approaches, involving a wide range of technologies. These include peptides, proteins, DNA vaccine, antigens delivered with viral vectors and ex vivo expanded dendritic cells, as well as genetically modified cells. Important lessons have been learned from these early studies which indicated that the targeted antigen, especially when using a peptide-based vaccine, can be down-regulated following vaccination, a fact which strongly suggests that single antigen vaccines are unlikely to be of use in melanoma [7]. Nevertheless, there are still a number of single antigen/epitope vaccines in clinical trials where the results have yet to be announced.

other tumor types

prostate cancer

The fact that melanoma is so unpredictable and chaotic suggested the possibility of applying the cancer vaccine technique to tumors that were slower growing and much more predictable in their spread. One which stands out is prostate cancer with its eponymous specific antigens. There are now several vaccine approaches targeting hormone-resistant prostate cancer. The most advanced of these is a dendritic cell-based vaccine, commercialized by Dendreon Corporation, who pulse the patient’s autologous dendritic cells with a recombinant fusion protein comprised of prostatic acid phosphatase antigen and granulocyte-macrophage colony-stimulating factor (GM-CSF). Two randomized studies failed to achieve the primary endpoints, although last year the discovery that survival in the vaccine arm was significantly longer than expected compared with the placebo led to an attempt to register the vaccine with the Food and Drug Administration (FDA) [8]. More data will be required if the FDA are to approve this vaccine. It is interesting that the only logical explanation of these data is that the vaccine primes for the inevitable docetaxel, which all the patients eventually
received, and that there is a synergy between the vaccine and subsequent therapy. In this regard there are many examples of this in the literature, particularly with regard to the use of radiotherapy [9].

Other trials involve the use of cell-based vaccines and these are now in randomized studies. Onyxvac, a British biotech company, has used three allogeneic prostate cell lines following preclinical data indicating that these could often be more effective than autologous cell lines which are clearly not practical for prostate cancer [10]. In a phase IIa study, Michael et al. showed that ~40% of patients had a response, in that the rate of rise of prostate-specific antigen (PSA) slowed significantly following vaccination and that this correlates with cell-mediated cytokine analyses and time-to-progression [11]. This vaccine has now progressed to a randomized phase IIb study. Cell Genesys Inc. have used a similar approach in which the cells express GM-CSF as an adjuvant. Again, very good phase II data have been presented but no phase III data are available at the time of writing (reviewed in [12]). Therion, using a recombinant attenuated vaccinia virus and boosting with a fowlpox virus expressing PSA and the B7.1 co-stimulatory molecule, has shown very encouraging phase II data [13]. Importantly, it was shown to significantly improve the outcome when used before the introduction of hormone therapy, as opposed to hormone therapy followed by vaccine, the second modality being added when the PSA continued to rise at 6 months. There was a significant increase in median time-to-treatment failure in favour of the vaccine followed by endocrine arm thus once again highlighting the potential of synergy with subsequent therapies. Unfortunately, Therion has gone into administration following the failure of a pancreatic cancer vaccine and the technology is being licensed out to another company.

In addition to the above there are many other candidates targeting prostate cancer and they include other approaches using dendritic cells, peptides, proteins and DNA-based vaccines. It is likely that by the end of 2008 there will be several announcements of the success, or failure, of these and other approaches. The data to date strongly suggest that even if these agents fail to make their major endpoint then combination and sequential therapy needs to be actively considered and trialled [13].

lung cancer

*Mycobacterium vaccae* (also known as SRL-172) has been used as a vaccine in lung cancer along with standard chemotherapy. Very encouraging single institute led to a multicentre randomized study in which no significant survival benefit was seen for the vaccine arm versus the placebo. Subsequent analyses of this study showed that only approximately half the patients had the vaccine injected intra-dermally, as opposed to subcutaneously, and only half had three or more vaccines when the protocol called for repeated injections. In spite of this there was a significant improvement in the side-effects of chemotherapy and quality of life in those who received the vaccine compared with the placebo [14]. Moreover, an ongoing analysis suggests a survival benefit in the adenocarcinoma subgroup [15]. This study highlights the problems of taking a new technology out to multiple centers not familiar with the ethos of the dose and administration.

Another lung cancer vaccine, based on MUC-1, known as L-BLP25, is a vaccine strategy that targets the exposed core peptide of MUC-1 and which in a randomized phase II study, where the vaccine is given after normal care for stage IIIB and IV non-small-cell lung cancer patients on a randomized basis versus best supportive care, ongoing analysis of this study shows a strong survival trend in favor of the vaccine arm, 30.6 versus 13.3 months, in a subgroup of patients with loco-regional stage IIIB disease [16]. There are a variety of other vaccine approaches, including other peptides targeting the human telomerase reverse transcriptase (TERT), as well as approaches using dendritic cell-based vaccine schedules.

colorectal cancer

Heriot et al. and Evans et al. have shown how systemically immunosuppressive even small colorectal cancers can be and that this is reversed upon complete excision of the tumor [17, 18]. An autologous colorectal cancer vaccine candidate has produced clinical benefit in a randomized study, published in the *Lancet* [19]. Autologous-based vaccines require tremendous infrastructure and are at all times bespoke with several patients unable to receive a vaccine due to the failure to grow autologous cells *in vitro*. A number of other approaches are in development, including dendritic cells pulsed with multiple peptides and single target vaccines such as those against ST4 (for example Trovax), TS-1 and other candidates. The problem is that the best data to date are in Duke’s B cancer, thus necessitating very long studies, or in minimal residual disease. However, the glut of new therapeutic agents in colorectal cancer makes such vaccine studies difficult to pursue in the absence of a combination approach.

breast cancer

There are a number of encouraging candidates in breast cancer, with a vaccine based on the HER2/neu. E75 peptide, reducing the risk of recurrence by 50% in 101 breast cancer patients who were clinically free at 20 months after treatment, compared with those who were not treated with the vaccine [20]. Other candidates based on the MUC antigen and telomerase are also in development. Another approach is to use synthetic ganglioside-based vaccine as is being developed in Cuba with good provisional results requiring further study.

other tumors

Whereas a few years ago the only serious vaccine attempts were targeted at melanoma, there now appears to be no tumor type that is exempt from being considered as a suitable target for immunotherapy and cancer vaccination. These include renal, pancreas, ovary, lymphoma, brain, sarcomas, pediatric tumors and leukemias. Some of these are being targeted with the same vaccines, such as the ST4/Trovax, which has been used in both colorectal and renal cancer, as well as an antigen initially used for melanoma but also found on other solid tumors, such as lung, i.e. the NY-ESO antigen. It is expected
that some of these studies will have matured by the latter part of 2008.

future development

It has become increasingly evident that one of the main problems with cancer vaccine development is that the tumors are already very resistant to an immune response, sprouting many immunological shields and secreting immunosuppressive cytokines. The obvious way to address this is to remove the tumors completely but this is not always possible. Vaccines may be most suitable in a non-macroscopic disease situation but lessons from melanoma vaccine studies after full resection suggest that an effective vaccine, that induces a specific immune response, may ultimately fail to provide clinical benefit because of down-regulation of tumor antigens and subsequent resistance. In non-resectable tumors the defense shields can be targeted using specific antibodies and ligands, such as CD55, and inhibitors of suppressive cytokines, such as transforming growth factor (TGF)-β. However, much of this action is due to the infiltration of myeloid suppressor cells and T-regulatory cells, both of which contribute to the defense of the tumor against an immune attack. The unexpected synergy between certain chemotherapies and vaccines may well be due to the ability of some chemotherapies to inhibit myeloid suppressive cells (gemcitabine) and other low-dose chemotherapies to inhibit T-regulatory cells, such as cyclophosphamide and lenalidomide. The way forward is to identify the optimal combinations to try to induce a synergistic response and the order in which these are given will be very important.

It is well established that priming the immune response by a number of mechanisms, from BCG, vaccines and interleukin (IL)-2, will enhance the subsequent response to radiotherapy. It is also becoming clear that the destruction of cells by radiotherapy or radiofrequency ablation may shed tumor antigens, which are taken up by the immune system, and post-treatment vaccination and immune stimulation, such as with low dose IL-2 can induce an effective clinical response.

conclusion and future directions

There is too much good phase II data, some of it randomized, to discard the development of cancer vaccines just because phase III studies have yet to deliver a registrable product. What is clear is that the correct patient population, with the right tumor type, at the right stage in the right sequential phase with regard to other treatment modalities must be selected. Although there are many different tumor antigens being targeted, either alone or in combination, as well as a broad range of technologies, no one specific antigen or sets of tumor antigens, nor specific technology has established a commanding lead. The first vaccine to get registered for whatever indication will ignite a tremendous increase in interest in this area as the advantage of being relatively non-toxic and enhancing the effect of other modalities, while reducing the side-effects of chemotherapy, are much appreciated by the patients. I believe it is the ability to enhance responses to other modalities that will make cancer vaccine technologies indispensable in the future.

The ability to spot the optimal combination of modalities at the right stage of disease, also with the right biomarkers that may be able to detect those patients who are unlikely to respond to this therapy, together the judicious use of sequential therapy, and taking this into account for trials that require survival to be a major endpoint, will be crucial in obtaining the best possible results.

disclosures

Angus C. Dalgleish is Research Director of Onyxvax, a biotech company with a prostate vaccine in phase IIB trials.

references