Editorial

The Unfulfilled Promise of Melanoma Vaccines

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INTRODUCTION

There is a sense of impatience with the unfulfilled, decades-long promise of melanoma vaccines. The promise is kept alive by a series of encouraging small trials such as the randomized trial reported by Bystryn et al. (1) in this issue, by remarkable progress in the molecular definition of human melanoma antigens recognized by the immune system, and by opportunities for vaccine construction arising from elucidation of the structural basis for presentation and recognition of these antigens by the immune system. These melanoma antigens include cell surface gangliosides GM2, GD2, and GD3; melanosomal differentiation antigens such as MelanA/MART-1, gp100, and tyrosinase; antigens expressed in melanomas and testes such as the NY-ESO-1 and MAGE family of cancer-testes antigens; and several melanoma antigens that are unique to single patients’ melanoma cells (reviewed in Refs. 2–4).

Awareness of both the structure of the target melanoma antigen and the nature of the desired immune response is the logical starting point for tumor vaccine development. The ease of serological analysis has facilitated development of vaccines aimed at inducing antibodies. Currently, for melanoma gangliosides (as for a range of bacterial cell surface antigens), there is a single optimal approach to vaccine construction aimed at inducing antibodies, chemical conjugation of the antigen to a large, highly immunogenic carrier protein, plus the use of a potent immunological adjuvant (reviewed in Ref. 5). Options for augmenting the immunogenicity of T-cell antigens are more varied (reviewed in Refs. 3 and 4). For the melanosomal and cancer-testes antigens, these options include: (a) the full proteins or MHC-restricted peptides modified by amino acid substitutions to increase immunogenicity; (b) genes or minigenes for these proteins or peptides used as DNA vaccines; or (c) these genes expressed in viral or bacterial vectors. Costimulatory molecules or cytokines can be incorporated into these vaccines, and most of these approaches can be applied to expressing these antigens in antigen-presenting cells, such as dendritic cells, that are then used to vaccinate the patient. Furthermore, because most tumor-rejection antigens in experimental animals are individually unique (mutated), a variety of individualized vaccines are being tested. Whole cell vaccines can be prepared from each patient’s melanoma (if the tumor specimen is large enough), and immunogenicity may be increased by the use of an immunological adjuvant and transduction with genes for cytokines or costimulatory molecules or by treatment with hapten, such as dinitrophenyl. Other approaches to increasing the immunogenicity of unique and shared melanoma antigens include the use of heat shock proteins that may carry the full range of melanoma cell peptides, and DNA or mRNA vaccines, each of which may be obtained from smaller biopsy specimens. The range of options for augmenting T-cell immunity against melanomas is daunting. Clinical trials with each of these second generation approaches to augmenting T-cell immunity are recently completed, ongoing, or planned. There is no basis for selecting one over the other at this time.

The low immunogenicity of tumor antigens and the heterogeneity of antigen expression on different melanomas and different melanoma cells within the same patient can be addressed by the use of combinations of the highly immunogenic, second generation vaccines, but there are other, more perplexing obstacles relating to the tumor/host environment (reviewed in Ref. 4). These are probably the result of Darwinian responses by tumor cells to a hostile environment. Tumor cells may fail to express relevant antigens to the immune system and may suppress the immune response, each by a variety of mechanisms. Clearly vaccine trials conducted to date have only begun to address the questions that will need to be answered before melanoma vaccinology can realize its potential. Nevertheless, pressure resulting from impatience with the pace of progress is palpable and threatens to interfere at a time of extraordinary opportunity. Establishment of proof of principal by a positive large randomized trial with a melanoma vaccine would ease this pressure and facilitate progress on all fronts.

The main advantage to the cell or cell fraction vaccines used in clinical trials over the last 30 years, and in the study by Bystryn et al. in this issue, is the broad range of antigens expressed. These have resulted in occasional clinical responses in patients with measurable melanoma and occasional improvement in the disease-free interval in patients treated in the adjuvant setting (reviewed in Ref. 6). Because these trials were generally conducted in small numbers of patients and consistent immune responses were either not induced or not tested for, they provided neither a firm foundation for the development of increasingly immunogenetic and effective vaccines nor a convincing proof of principal. The result described in this issue by Bystryn et al. (1) with a shed antigen vaccine is an encouraging addition to this series of first generation vaccine studies. Patients receiving the shed antigen vaccine had a significant increase in the median time to recurrence from 0.6 years to 1.6 years, and the percentage of patients alive at 3 years increased from 33 to 53%. The risk factors were comparable in the two groups; however, there is cause for caution in interpreting these results, as the investigators note. This trial involved only 38 patients in total. A swing of only 3 patients would equalize the survival

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rates at 3 years or the disease-free interval rate at 2 years. Comparison of these results to other trials is precluded by unique entry criteria requiring ≥1 clinically positive node or ≥2 microscopically positive nodes. Given the lack of toxicity of this vaccine, it is unfortunate that it was not possible to complete the originally intended level of patient accrual. Bystryn et al. have identified a series of antigens recognized by immune sera and peripheral blood lymphocytes from vaccinated patients (7), so an added benefit to accrual of a larger number of patients might have been the correlation of clinical outcome with particular immune responses against particular antigens.

Four large randomized Phase III trials with melanoma vaccines are currently being conducted in the adjuvant setting, one by the Eastern Clinical Oncology Group with a GM2 conjugate vaccine compared to high dose interferon (8), one by the Southwest Oncology Group with a melanoma cell lysate vaccine (Melacine, Ref. 9) compared to placebo and the third with an allogeneic melanoma cell vaccine by the John Wayne Cancer Institute (CancerVax, Ref. 10) compared to placebo. Early results of the GM2 trial have recently been published (8) and results of the Melacine trial have been presented. While antibody responses against GM2 correlated with an improved prognosis, disease free and overall survival at a median follow-up of 18 months were significantly superior for patients treated with interferon compared to those treated with the GM2 vaccine. Longer follow-up is clearly needed, but these results suggest that induction of antibodies against GM2 alone may not be sufficient for induction of clinical benefit. Trials with a trivalent GM2, GD2, and GD3 vaccine are planned based on the finding that only 25% of melanoma cell lines can be lysed in the presence of GM2 antibody plus complement while >90% of cell lines can be lysed with a mixture of antibodies against GM2, GD2, and GD3. The Melacine trial was conducted in Stage II melanoma patients. It demonstrated a significant improvement in disease free interval, or not, depending on whether an intent to treat or an eligible patients only analysis was performed. Further follow-up of this encouraging trial to determine impact on overall survival is pending. The CancerVax trial is still ongoing. It offers the additional promise of being able to correlate particular antibody and T-cell responses against particular antigens with clinical outcome, information that could quickly translate into the use of these antigens in more immunogenic, second generation, vaccines. The fourth randomized trial is ongoing and involves an autologous DNP modified melanoma cell vaccine (M-VAX). While nothing is known about immune recognition of any particular antigen in this vaccine, it is intriguing that it has induced inflammation at metastatic sites distant from the area of injection (11).

The promise of melanoma vaccines has been hinted at for 40 years by a long series of small trials with first generation melanoma cell or cell fraction vaccines, such as the encouraging result presented by Bystryn et al. (1) in this issue. The two currently ongoing large Phase III trials with allogeneic (CancerVax) and autologous (modified melanoma cell vaccine) vaccines represent the culmination of these first generation investigations. Regardless of their outcome, the third generation of antigen-specific vaccines, which include optimal second generation vaccines used in combination, offers enormous promise because it combines polyvalency with significantly increased immunogenicity. The promise of melanoma vaccines remains unfulfilled but more soundly based and alluring than ever.

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