Vaccine Therapy for Patients With Melanoma

Haigh et al provide thoughtful, detailed summary of 3 decades of intensive work aimed at developing active, specific immuno-therapies (vaccines) for patients with melanoma. However, as the 20th century draws to a close, the key question is: Can any vaccine be considered an effective therapy for patients with melanoma? To rephrase the question: What constitutes proof of efficacy for a melanoma vaccine, and have any vaccines met those criteria? In a word, the answer to the first question is “no.” The answer to the second question, however, requires more elaboration.

What Constitutes Proof of Efficacy?

To date, melanoma vaccines have been used in two settings: First, these vaccines have been employed in patients with measurable, metastatic disease. In this setting, proof of efficacy (objectively defined as tumor regression of ≥50% of the sum of perpendicular diameters of measured lesions, without any new or progressing lesions) is relatively straightforward and can be determined in phase II trials. Both autologous and allogeneic melanoma vaccines have been associated with low levels of antitumor response; no series has reported an objective response rate as high as 10%. Alternatively, vaccines could prove to be efficacious in prolonging survival and/or improving quality of life in patients with advanced disease in the absence of objective tumor regression. One phase III clinical trial has compared an allogeneic melanoma cell lysate (Melacine; RIBI Immunochem, Hamilton, Montana) to multiagent chemotherapy (the so-called Dartmouth regimen).[1] Survival in patients receiving the vaccine was slightly shorter than that in patients given chemotherapy. Without an untreated control group, however, it is impossible to determine whether either therapy was associated with a significant improvement in survival. That limitation notwithstanding, the relatively poor response and survival rates associated with the Dartmouth regimen in a series of recent phase II and III trials[2-4] call into question whether the vaccine-treated patients fared any better than they might have had they not received any treatment whatsoever.

It stands to reason that melanoma vaccines might work best when the tumor burden is lowest. Recognizing this, most clinical trials have focused on the use of vaccines in the adjuvant setting, after resection of all known disease. In this setting, there is only one unequivocal criterion for efficacy: demonstration of improved survival in vaccine-treated patients in at least one phase III trial. No surrogates or intermediate end points can substitute for this criterion, and phase II trials comparing vaccine-treated patients to historical controls have no value at all.

If there were ever any doubt as to the unsuitability of historical controls in resected patients with melanoma, that doubt should be put to rest by the results of two consecutive cooperative group adjuvant trials (E1684 and E1690/S9111/C9190).[5,6] These two studies were initiated only 6 years apart and had nearly identical eligibility criteria. Nevertheless, the survival of the untreated control groups differed dramatically: In the more recent study, the control group had a 67% improvement in survival, even though the surgical and postsurgical treatments were the same. If such similar groups can differ so markedly after so short a time, it is obvious that comparisons to historical controls can never substitute for prospective comparisons. Of course, based on this strict definition, no vaccine has demonstrated efficacy in improving survival in the adjuvant setting.

Ultimately, perhaps, new vaccines will actually prevent melanoma development, as opposed to preventing melanoma recurrence in patients who have already been treated surgically. Proof of efficacy in this setting must be equally stringent; namely, demonstration of a decrease in the
incidence of melanoma (and preferably a decrease in melanoma-related deaths) in at least one phase III trial involving individuals who are genotypically, phenotypically, or environmentally at high risk of melanoma development.

Criteria for Testing Melanoma Vaccines in Phase III Trials
For the immediate future, the key question has become: Which vaccine, or vaccines, shows sufficient promise to be tested in phase III trials? In the past, phase III adjuvant trials involving vaccines had various rationales. A vaccinia viral lysate of melanoma cells has been evaluated in two phase III trials, both of which found no improvement in overall survival.[7,8] The main rationale for this trial consisted of single-institution data showing a marked improvement in disease-free survival when vaccinia lysate-treated patients were compared to historical controls.

The two phase III trials of an allogeneic melanoma vaccine conducted at the John Wayne Cancer Institute, described in detail by Haigh et al, were also supported by phase II data suggesting improved survival compared to historical controls. The phase II experience with this allogeneic vaccine, however, far exceeds that accumulated with vaccinia oncolysates. Furthermore, the John Wayne trials were based on a great deal more correlative immunologic data than were available with previous vaccines.

Another allogeneic melanoma vaccine, this one a whole-cell lysate, has undergone phase III testing by the Southwest Oncology Group (SWOG-9035) in patients with intermediate-thickness, node-negative melanoma. The compelling rationale for choosing this vaccine was the low but definite level of antitumor activity exhibited by the vaccine in advanced disease. The amount of antitumor activity that must be demonstrated in stage IV melanoma before an immunomodulatory approach should be considered for the adjuvant setting has not been defined. Indeed, the ganglioside vaccine GM2-KLH has not been tested extensively in patients with stage IV melanoma; instead, it went directly into adjuvant trials. Both the United States intergroup (Eastern Cooperative Oncology Group [ECOG] and SWOG) and the European Organization for Research and Treatment of Cancer (EORTC) are testing this vaccine in phase III trials.

The compelling rationale for the GM2-KLH vaccine came from a small, randomized pilot trial suggesting an improved outcome in patients treated with the GM2 ganglioside vaccine plus bacillus Calmette-Guérin (BCG), as compared with patients receiving BCG alone. The GM2-KLH conjugate was found to be better at stimulating a humoral immune response than GM2 plus BCG; hence, this vaccine is being utilized in the cooperative group trials.

The ability to monitor the immune response based on a simple blood test is another attractive aspect of the GM2 ganglioside vaccine. In contrast, it is more difficult to determine whether a relevant immune response has occurred following vaccination with whole-cell vaccines or peptide antigens. This is germane to the SWOG-9035 trial: If the results of this trial are negative, it will be difficult to determine whether the failure of the vaccine is due to inadequate induction of a necessary immune response or inability of the induced immune response to prevent recurrence.

Which Vaccines Should Be Tested Next in Phase III Trials?
The plethora of vaccines now becoming available for melanoma patients, combined with the resources required for phase III adjuvant trials, means that hard choices must be made when evaluating candidate vaccines for next-generation clinical trials. Of the vaccine strategies outlined by Haigh et al, the one least suited for cooperative group clinical trials is autologous tumor vaccination. Autologous tumor vaccination, at least as currently employed, also is not a viable option for the large majority of patients whose melanoma is diagnosed at stages where bulky tumor is not available (eg, node-negative patients or those with microscopically positive sentinel lymph nodes).

Allogeneic melanoma vaccines are currently the subject of four ongoing or recently completed multi-institutional trials. It is worth debating whether more resources should be committed to allogeneic vaccine research before the results of the current crop of studies become available. Certainly, at least one other allogeneic vaccination approach (the shed antigen vaccine of Bystryn) has supportive clinical and preclinical data comparable to the data supporting the vaccines already in phase III trials.[9] In many ways, however, it is the various defined antigen vaccination strategies that are in greatest need of prioritization.

Peptide antigens hold great promise but are often restricted to a subset of the available patient population. (For example, many currently available peptides can be used only in HLA-A2-positive patients, who account for only about 50% of the total melanoma population.) Furthermore, monitoring the adequacy of the T-cell response to peptide antigens remains a challenge. Moreover, even if the T-cell response can be reliably monitored, we do not yet know which responses actually correlate with efficacy. Knowledge of this information would help resolve other vexing problems—defining the optimal dose, route of administration, and immunologic adjuvant therapy to
use in phase III peptide antigen trials.
For now, it seems that more phase II data are required to make informed choices about phase III testing of peptide antigens. Innovative, randomized, phase II trials with extensive biological correlations seem to be most likely to move the field forward. In this regard, a noteworthy example is a randomized trial being conducted by Rosenberg et al at the National Cancer Institute. This trial is randomizing stage IV melanoma patients to high-dose interleukin-2 (IL-2 [Proleukin]) alone vs high-dose IL-2 plus peptide antigen vaccination.

The ganglioside antigen vaccines avoid some of the problems associated with peptides: Ganglioside vaccines are not major histocompatibility complex (MHC) restricted; hence, there is no need for strict eligibility criteria. Monitoring immunoglobulin levels is relatively straightforward. However, there is no consensus about what type of immunoglobulin response (IgG or IgM) is best, or even whether any immune response that is directed at a single antigen, no matter how strong, can lead to a meaningful improvement in survival. Nonetheless, we believe that more studies of various ganglioside vaccines are warranted, particularly vaccines that generate a strong IgG antibody response.

Anti-idiotype Antibodies
In this regard, another vaccination strategy not mentioned by Haigh et al deserves attention. Anti-idiotype antibodies, although not vaccines in the classic sense of the word, do offer the promise of generating high levels of IgG antibody against otherwise difficult immunogens. Emerging data indicate that high IgG levels against ganglioside GD2 can be achieved with anti-idiotype antibodies, and that these levels may have some meaningful benefit against advanced disease. In view of these data, we believe that anti-idiotype antibodies derived from anti-GD2 primary antibodies are strong contenders for evaluation in the adjuvant setting in melanoma.[10]

Moreover, a significant number of gangliosides are present on melanoma cells. Ultimately, it may be possible to use multiple anti-idiotype antibodies (or combinations of antibodies with other antigens) in a cocktail that would circumvent the problems of both antigenic heterogeneity and modulation, which may limit single-antigen vaccination strategies.

New Areas of Investigation
New areas of investigation include vaccination with dendritic cells and genetically modified vaccines. Dendritic cells are potent antigen-presenting cells that can initiate immune responsiveness in naïve or resting T cells. Dendritic cells can be induced to present tumor-associated antigens by pulsing them in vitro with whole tumor cells, tumor lysates, or peptide antigen fragments; or by transfection with plasmids encoding tumor antigens. Preclinical models have demonstrated that the administration of antigen-pulsed dendritic cells can mediate the regression of large, established tumors[11] — a feat beyond the capability of most in vivo vaccination models. The use of antigen-pulsed dendritic cells is currently being evaluated in phase I and II trials at several different institutions.

Genetically modified vaccines are also being explored. Plasmid-encoding tumor antigens are being investigated in a variety of viral and nonviral vectors in attempts to stimulate immune responses. Cytokine genes, notably IL-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF), are also being utilized as an adjuvant therapy that is administered locally at the site of vaccinations. Clearly, both dendritic and genetically modified vaccines are in the developmental stage. Nonetheless, they represent new technologies that can augment the immune response beyond that achievable with current vaccines.

Which Patients Should Comprise the Control Group in Future Trials?
The choice of a treatment arm for adjuvant trials in melanoma is not the only current area of controversy. The choice of the control arm can be difficult as well. For patients with positive nodes or thick primary tumors, high-dose interferon alfa-2b (Intron A) has received FDA approval and is widely used as standard adjuvant therapy. Recognizing the uncertainties that remain about the magnitude of any survival benefit associated with high-dose interferon, it is still an appropriate reference standard for the control arm of phase III trials involving patients with node-positive or thick node-negative disease.

That is not to say that interferon-alfa-2b must be the control arm of such studies. However, if interferon is not used as the control arm in relevant patient populations, how will we know whether an active treatment is more active than our current standard without a head-to-head comparison? Conversely, what if a vaccine-treated group and an interferon-alfa control group were to have similar survival rates? Could we reasonably conclude that the vaccine is as effective as interferon and that it should become the standard of care? Or should we conclude that both the vaccine and interferon have no impact on survival, and that neither should be used? This precise situation could arise if the
current US intergroup trial comparing the GM2-KLH vaccine to high-dose interferon-alfa-2b shows no survival difference between the treatment arms. In situations in which interferon is not used as the control arm (including patient populations in whom interferon is not currently indicated), it seems that the best control arm would be a no-treatment or observation arm. Even this statement is controversial, however: The John Wayne trials are using BCG plus a placebo as the control arm.

**Needed: Clinical Trials With Meaningful End Points**

The progress outlined in the report by Haigh et al is the direct result of the commitment of a small cadre of investigators to the goal of finding new approaches to the treatment of melanoma. Proving the value of these vaccines, as well as other immunologic advances that have yet to be developed, will require an equally strong commitment, as we enter the new millennium, to conduct carefully designed, phase II and III clinical trials. Phase II trials should not evaluate tumor response as the primary end point. Instead, these trials should evaluate measurable immunologic end points, such as cellular reactivity to tumor-associated antigens.[12] Randomized, phase II clinical trials can help evaluate important unanswered questions, such as the most appropriate dosage, route of administration, immunologic adjuvant therapy, and antigen source. These clinical trials will help define appropriate candidate vaccines for large-scale, phase III trials in patients with resected melanoma. Phase III trials will take years and thousands of patients to conduct, but they are the only way that the seemingly simple questions posed at the outset of this commentary will be answered definitively. It is fitting that the researchers at the John Wayne Cancer Institute, most notably, Donald Morton, have demonstrated the commitment to put their vaccine to this ultimate test.

**References:**


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