Vaccine Therapy for Patients With Melanoma

Review Article

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Investigation into the therapeutic use of vaccines in patients with metastatic melanoma is critically important because of the lack of effective conventional modalities. The most extensively studied melanoma vaccines in clinical trials are whole-cell preparations or cell lysates that contain multiple antigens capable of stimulating an immune response. Unfortunately, in the majority of studies, immune responses to these vaccines have not translated into a survival advantage. Advances in tumor cell immunology have led to the identification of candidate tumor cell antigens that can stimulate an immune response; this, in turn, has allowed for refinements in vaccine design. However, the exact tumor antigens that should be targeted with a specific vaccine are unknown. The univalent antigen vaccines, which have greater purity, ease of manufacturing, and reproducibility compared with polyvalent vaccines, may suffer from poorer efficacy due to immunoselection and appearance of antigen-negative clones within the tumor. Novel approaches to vaccine design using gene transfection with cytokines and dendritic cells are all promising. However, the induction of immune responses does not necessarily confer a therapeutic benefit. Therefore, these elegant newer strategies need to be studied in carefully designed clinical trials so that outcomes can be compared objectively with standard therapy. If survival is improved with these vaccine approaches, their ease of administration and lack of toxicity will firmly entrench active specific vaccine immunotherapy as a standard modality in the treatment of the melanoma patient.[ONCOLOGY 13(11):1561-1574, 1999].

Introduction

Currently, the only curative treatment for primary melanoma is surgical excision. The thickness of the primary melanoma is the most important prognostic factor governing outcome in patients who do not have nodal disease. Patients with thin melanomas (American Joint Committee on Cancer [AJCC] stage I disease) have an excellent prognosis after surgical excision with adequate margins. However, in patients who have a melanoma thicker than 4 mm, nodal disease, or satellitosis (AJCC stage III disease), the rate of systemic recurrence is high, and prognosis is far worse; these patients have a 10-year survival rate of 20% to 40% after lymphadenectomy.[1]

Postsurgical adjuvant therapy is important in patients who are at a high risk of relapse. Adjuvant radiotherapy or chemotherapy, has not had a substantial therapeutic impact in these patients, however.

Biological therapy using interferon-alfa-2b (Intron A) as a post surgical adjuvant has shown benefit in patients with node-positive melanoma in an Eastern Cooperative Oncology Group trial (EST 1684).[2] This study demonstrated that therapy with interferon-alfa-2b after complete resection of nodal metastases improved disease-free survival from 1 to 1.7 years, compared with observation, and also increased overall survival from 2.8 to 3.8 years. Unfortunately, recently presented results of the confirmatory intergroup trial (EST 1690) found no survival benefit from either high- or low-dose interferon, compared with observation; relapse-free survival was improved in the group treated with high-dose interferon, but there was no improvement in overall survival because delayed high-dose interferon administered after recurrence appeared to provide equivalent benefit.[3]

Responses to chemotherapy in patients who have AJCC stage IV melanoma are also typically poor. Combination chemotherapy with or without biological therapy using interleukin or interferon, while achieving encouraging response rates, has not increased median survival compared to that achieved with single-agent dacarbazine (DTIC-Dome).[4-6] This lack of a survival benefit of combination regimens, coupled with their considerable systemic toxicity, indicate that alternative therapeutic approaches are urgently needed for patients with metastatic melanoma.

Immunotherapy as an adjuvant after surgical resection for stage III melanoma, or as primary therapy for AJCC stage IV disease, is receiving more attention because of exciting data from animal
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models.[7,8] Active specific immunotherapy using a vaccine has great appeal because of evidence that melanoma may respond to vaccines, without the toxicity that accompanies more conventional regimens. Encouraging results from phase II trials have paved the way for pivotal, phase III, randomized, controlled trials.

In the near future, research on cancer vaccines may finally provide dividends and make active specific immunotherapy a standard regimen for patients with high-risk melanoma. This review addresses the principles of cancer immunity and the goals of vaccine therapy; focuses on the results of clinical trials using different melanoma vaccines; and outlines novel approaches and future directions in melanoma immunotherapy.

Immunotherapeutic Methods

Biological therapy is the use of natural physiologic substances produced by the cells of the immune system for treatment designed to enhance natural host defenses in order to produce an antitumor effect. Immunotherapy, one type of biological therapy, can be categorized into active and passive approaches.

Active immunotherapy is the use of agents that will cause the host to mount an immune response, which will lead to tumor cell growth arrest or death; this treatment can be further divided into specific or nonspecific methods. Specific immunotherapy, such as with tumor vaccines, is designed to elicit an immune response to one or more tumor antigens. Nonspecific agents, such as bacillus Calmette-Guérin (BCG) and levamisole (Ergamisol), and, more recently, cytokines, such as interferon and the interleukins, stimulate the immune system globally but do not recruit specific effector cells to produce antibodies or a T-cell response directed against a specific antigen.

In passive immunotherapy, agents, such as monoclonal antibodies and cells previously sensitized to host tumor antigens, are administered to a patient to directly or indirectly mediate tumor killing.

Vaccines and Tumor Immunity

Unlike prophylactic vaccines directed against infectious agents, cancer vaccines are used therapeutically in patients whose tumor cells have already successfully evaded host immunity prior to vaccination. It, therefore, remains a significant obstacle to generate an immune response to transformed cells that are inherently able to escape immune surveillance. This failure to develop endogenous immunity against cells that undergo transformation to the malignant phenotype may be due to many mechanisms, such as loss of major histocompatibility complex (MHC) expression or downregulation of antigen processing.[9,10]

It is apparent that, without costimulatory signals from proinflammatory cytokines during antigen recognition (which, for instance, are present during bacterial infection), T-cells may become tolerant to specific tumor antigens. The potential for a tumor to not only evade the immune system but also prevent that system from mounting an antitumor response by inducing tolerance is a serious concern in active immunotherapy.[11] In order for a vaccine to be effective, therefore, tolerance must be avoided or overcome.

The development of melanoma vaccines has included attempts to define the most relevant antigens that may induce an immune response, with the goal of developing a univalent or an oligovalent vaccine composed of a purified, synthetic, or recombinant antigen. Unfortunately, while some antigens have been shown to be immunogenic in melanoma patients, the data linking response to a particular antigen with extended survival is weak. In addition, it seems that an immune response against multiple antigens induced by a polyvalent vaccine would be more likely to result in maximal tumor cell kill because different cell clones with selective antigen loss reside within a mass of tumor tissue.

At present, it is also unclear whether a T-cell or B-cell response is the optimal effect to strive for with a cancer vaccine. More than likely, stimulation of both T- and B-cell reactivity is beneficial in different tumors. T-cells recognize antigenic peptides that are expressed in association with MHC molecules on the cell surface.[12] Both CD8+ T-cells, which recognize peptides bound to MHC class I molecules, and CD4+ T-cells, which recognize peptides bound to MHC class II molecules, are important for optimal cytotoxic and cytokine effector responses.

Since antigen recognition by T-lymphocytes depends on presentation of a peptide bound to a specific MHC molecule, peptides that do not bind to a host MHC molecule cannot produce a T-cell response. Therefore, only in patients of a specific human lymphocyte antigen (HLA) phenotype can a given peptide induce a significant immune response.

For example, MART-1/Melan-A is a well-defined protein antigen expressed by 80% of melanomas.
The immunodominant peptide binds to HLA-A2, which provides MHC restriction to this antigenic peptide. Since only 45% of Caucasians express HLA-A2, only 36% (80% of 45%) will benefit from a MART-1/Melan-A vaccine composed of the immunodominant peptide.[13]

To circumvent these problems, polyvalent vaccines have been developed that incorporate multiple antigens, which have complementary MHC restriction. Some of the known tumor antigens are listed in Table 1. These antigens are either tumor-associated antigens, which are shared by other tumors, or melanoma-associated antigens, which are found primarily in melanomas but also are seen in normal melanocytes.[14,15]

Some basic observations support the view that melanoma may be a good candidate for active specific immunotherapy. Approximately 15% of all melanomas present as metastases without clinical evidence of a primary tumor; such primaries have undergone regression, possibly due to destruction by cytotoxic T-lymphocytes.[13] Histopathologic evidence of tumor regression also has been frequently observed within primary melanoma specimens.[16,17]

Furthermore, antibodies against tumor antigens from patients with melanoma, as well as cytotoxic T-lymphocytes derived from the tumor tissue itself, can produce in vitro destruction of melanoma cells.[18,19] Cytotoxic T-lymphocytes from the blood of healthy volunteers, after priming with melanoma peptides or viruses encoded to produce specific melanoma antigens, have also been demonstrated to induce melanoma cell destruction.[20,21]

**Vaccine Design**

Many different vaccine strategies are under investigation. Each type of vaccine has distinct advantages and disadvantages that are attributable mainly to the number of antigens available as possible immunogens (Table 2).

Whole cells, either allogeneic or autologous, and either intact or lysed, contain many antigens on the cell surface, and theoretically have the greatest potential for eliciting an immune response directed against multiple antigenic targets. Newer vaccines, such as the specific peptide antigens, although highly purified and containing little extraneous material compared to whole cells, may lack the ability to incite effective immunity even if only a few tumor cells undergo antigenic modulation with loss of the particular antigen.

Immunization with autologous tumor cells has the advantage that it may induce an immune response against unique tumor-specific antigens caused by mutations within the patient’s tumor. A disadvantage of autologous vaccines is that the immunogen is an autologous tumor cell that has already evaded the host’s immune response and, therefore, may have downregulated its tumor antigens. Autologous tumor vaccines also are limited by the volume of tumor that can be harvested from a particular patient’s accessible tumor mass and the difficulty of manufacturing a “tailor-made” vaccine for each patient.

Allogeneic or synthetic vaccines rely on common shared antigens. An important advantage of peptide and other “defined” vaccines is their greater ease of manufacturing and quality control. The immune responses to vaccines also differ depending on their design. Peptide vaccines generally induce only a T-cell response and not a B-cell antibody response.[13] On the other hand, the GMK vaccine (the ganglioside GM2 coupled to a carrier protein, keyhole limpet hemocyanin [KLH], administered with an adjuvant) induces an antibody response only.[22,23] Allogeneic cellular vaccines have the ability to induce CD8+ and CD4+ T-lymphocyte responses,[24,25] as well as antibody responses.[26-28]

**Results of Vaccine Clinical Trials**

To date, no phase III, randomized, controlled trial has demonstrated a significant survival advantage in patients treated with a melanoma vaccine. However, many phase II clinical trials suggest that vaccine therapy may improve clinical outcome. The results of several ongoing phase III trials will help delineate more definitively the role that vaccines play in treating metastatic melanoma.

The following discussion summarizes the results of clinical trials of melanoma vaccines. The discussion is organized into categories based on the different types of vaccines currently under investigation, which are summarized in Table 3.

**Whole-Cell Vaccines**

Since we do not know the most relevant tumor antigen that will stimulate an effective immune response, whole-cell vaccines have the greatest potential to stimulate immune responses to many tumor antigens with different HLA profiles. Several whole-cell melanoma vaccines have been tested clinically.
CancerVax is a polyvalent whole-cell melanoma vaccine developed at the John Wayne Cancer Institute that is composed of three viable irradiated allogeneic melanoma cell lines. This composition was chosen for its high content of immunogenic melanoma- and tumor-associated antigens.[29] It is the most extensively studied vaccine currently under development.

An intradermal injection of CancerVax is administered biweekly for 12 weeks during the induction phase; adjuvant BCG accompanies the first two injections. Monthly injections are then continued for 1 year, followed by injections at 2- to 3-month intervals for up to 5 years.

Toxicity has been minor. Common toxicities include fatigue, myalgias, and local inflammatory skin reactions that are predominantly secondary to BCG. CancerVax has been used clinically in patients with AJCC stage III or IV melanoma. In phase II studies of 157 patients with stage IV melanoma, the median survival of patients treated with CancerVax was 23 months, which was significantly better than the 7.5-month median survival in historical controls who received other therapies.[30] The greatest survival advantage was seen in those who underwent resection of all clinically detectable disease prior to beginning vaccine therapy.

A subsequent study evaluated the effect of CancerVax in 88 patients with stage IV melanoma who were matched, according to gender and organ involvement, with 88 controls. All patients underwent complete resection of metastatic disease prior to vaccination. Patients treated with CancerVax had a 5-year survival rate of 40%, whereas the control group had a 5-year survival rate of 13%.[31] A strong humoral and cellular response to CancerVax has been correlated with improved survival in patients who have stage IV melanoma. If a pronounced delayed-type hypersensitivity response and an elevated level of immunoglobulin M (IgM) antibody to tumor antigen 90 (TA90) were present in treated patients, the 5-year overall survival was 75%, as compared with an overall survival rate of 8% in patients who had neither response (which was similar to untreated patients).[32] Finally, CancerVax has been shown to induce complete regression of in-transit metastases in some melanoma patients, with a median duration of complete remission of greater than 22 months.[32a] As a result of these findings, a multicenter, phase III trial comparing CancerVax with placebo in patients with stage IV melanoma who have undergone resection of all metastatic sites is in progress (Figure 1).

A survival benefit from CancerVax also has been demonstrated in phase II trials of patients with AJCC stage III melanoma. Median survival was greater than 80 months in the 283 patients who received CancerVax as an adjuvant therapy following lymphadenectomy for palpable nodal disease, as compared with 24 months in 1,474 historical control patients who received other conventional therapies after lymphadenectomy.[26] As in stage IV disease, a significant delayed type hypersensitivity response and humoral response with elevated anti-TA90 IgM titers correlated with an improvement in survival.[33]

A multicenter, randomized, controlled trial comparing CancerVax vs interferon-alpha following complete lymphadenectomy in stage III patients began in early 1998. However, since the negative results of the EST 1690 trial were reported, the interferon arm has been changed to a control arm consisting of BCG plus placebo. Since BCG has been shown to have some activity in melanoma,[34,35] this trial will allow us to distinguish between the nonspecific effects of BCG alone and specific immunization to melanoma-associated tumor antigens (Figure 2).

Autologous Melanoma Vaccine—Another approach to the whole-cell melanoma vaccine is the use of autologous tumor cells, typified by the autologous melanoma vaccine of Berd and Mastrangelo,[36] which was modified from the work of Peters et al.[37] Autologous vaccines use the patient's own tumor as the antigen source. In a study of 64 patients with metastatic melanoma, autologous tumor cell vaccine was administered with adjuvant BCG after low-dose cyclophosphamide (Cytoxan, Neosar); clinical responses were observed in 12.5% of treated patients.[38] The same autologous vaccine was modified with the hapten dinitrophenyl to enhance response and was administered to 62 patients with palpable nodal disease after standard lymphadenectomy. Median overall survival was over 62 months, which compared favorably with reported survival durations from historical surgical series.[39] An important finding in this study was that a delayed-type hypersensitivity response to unmodified autologous melanoma cells correlated with a 71% 5-year survival rate following administration of the hapten dinitrophenyl vaccine, as compared with a rate of 49% in patients who had no delayed-type hypersensitivity response (P = .031).

Autologous vaccines require a large amount of tumor that is surgically accessible for removal in order to retrieve enough cells to prepare the vaccines. Logistic problems relating to the production of sufficient quantities of autologous vaccine needed for larger clinical trials continue to challenge research in this field.
Lysate Vaccines
Lysate vaccines, such as the vaccine developed by Mitchell et al, are produced by mechanically disrupting whole melanoma cells.[40] These lysates can also be augmented with nonpathogenic viruses, such as vaccinia, used by Wallack,[41] or Hersey.[42] Lysate vaccines are characterized by the presence of multiple tumor antigens and, therefore, have the potential for enhancing a polyvalent immune response. However, lysate vaccines do not appear to be as immunogenic as living whole-cell vaccines.

Vaccinia Melanoma Oncolysate—Wallack and colleagues engineered a vaccinia melanoma oncolysate vaccine by infecting four allogeneic melanoma cell lines with live vaccinia virus; after sonification and separation, the virus-enhanced cell membranes are used in the vaccine. The vaccine is injected intradermally every week for 13 weeks at multiple sites near nodal basins; subsequent injections are administered every 2 weeks for 1 year.

A phase III, randomized, multicenter trial comparing vaccinia melanoma oncolysate with a vaccinia virus control in stage III melanoma demonstrated no significant difference in either disease-free or overall survival at a median follow-up of 46 months.[43] However, retrospective subset analysis suggested that, in 20 male patients age 44 to 57 years who had one to five positive nodes, vaccinia melanoma oncolysate provided a significant improvement in survival at 2, 3, and 5 years.

The overall lack of response to vaccinia melanoma oncolysate may have been due to several factors. First, the use of vaccinia virus as a control, rather than no treatment, may have confounded the results, as vaccinia virus alone has a therapeutic effect in patients with melanoma.[44] Second, vaccinia melanoma oncolysate therapy was administered for 1 year, which may not have been sufficient time to maintain immunoprotection. Finally, because the lysate was constructed from melanoma cell lines that did not express HLA-A2, tumoricidal cytotoxic T-cell activity may have been absent in HLA-A2–positive patients.

Vaccinia Melanoma Cell Lysate—The vaccinia melanoma cell lysate developed by Hersey is similar to vaccinia melanoma oncolysate except that the former consists of only a single melanoma cell line infected with vaccinia.[42] A phase II trial using vaccinia melanoma cell lysate and cyclophosphamide as an adjuvant in AJCC stage III melanoma patients resulted in a 5-year survival rate of 50%, as compared with 34% in historical controls.[45] Interim analysis of a phase III trial examining the clinical efficacy of vaccinia melanoma cell lysate has revealed a 19-month survival benefit of vaccinia melanoma cell lysate treatment, which was not statistically significant.[46]

Melacine, the lysate vaccine developed by Mitchell and colleagues consists of two homogenized melanoma cell lines that are combined with the adjuvant Detox (monophosphoryl lipid A and a purified mycobacterial cell-wall skeleton).[47] Melacine is administered subcutaneously weekly for 1 month, followed by an additional injection 2 weeks later. Patients who have responded clinically at 8 weeks receive five more injections over 6 weeks.[48]

In a trial of 139 patients with metastatic melanoma receiving Melacine, the median overall survival was 14 months, which compared to an expected survival of 6 to 8 months in untreated individuals.[49] In patients who responded or who had stable disease, however, the median survival was 22.3 months.[48]

A phase III study of 106 patients with AJCC stage IV melanoma compared Melacine vs chemotherapy with dacarbazine, cisplatin (Platinol), carmustine (BiCNU), and tamoxifen (Nolvadex).[50] Responses were fewer in the Melacine group. Median survival was 9.4 months for the group treated with Melacine, as opposed to 12.3 months for those treated with chemotherapy, which was not statistically different. Among the subset of patients who either had stable disease or who responded to treatment, median survival durations were 18.2 months with Melacine and 15.7 months with chemotherapy; again, this difference was not statistically significant. However, Melacine had much less toxicity than chemotherapy.[48]

The outcome of patients with stage II disease treated with Melacine vs observation alone in a recently concluded Southwest Oncology Group randomized trial (SWOG 9035) is awaited. A randomized, controlled trial using Melacine in resected stage III melanoma also is in progress.

Shed Antigen Vaccines
Shed antigen vaccines, another form of polyvalent antigen vaccine, are composed of surface molecules that are released by melanoma cells into the surrounding culture medium. Therefore, these vaccines are devoid of nuclear and cytoplasmic elements that may be superfluous to inciting an immune response. The potential advantage of shed antigen preparations over whole-cell and lysate vaccines is that multiple antigens, such as MAGE-1, MAGE-3, MelanA/MART-1, tyrosinase, and gp100, may be present in a vaccine that is easier to manufacture.[51]

The only shed antigen vaccine under clinical investigation, developed by Bystryn and associates,
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Combines shed antigens from three human melanoma cell lines and one hamster melanoma cell line.[52] In a phase II trial of 94 patients with resected stage III melanoma, patients treated with this vaccine had a disease-free survival of 30 months and a median overall survival of 5 years, both of which were 50% greater than survival durations in historical controls.[52] These results were the impetus for a phase III study that randomized patients with AJCC stage III melanoma after resection to receive either the shed antigen vaccine or a placebo (human albumin) vaccine. After 39 months, the median recurrence-free survival in treated patients was 18.6 months, as compared with 7.1 months in the placebo group.[53] Mortality at 2 years was 23% in treated patients and 40% in the placebo group. No toxicity was observed in either group. The results of this trial, although promising, are too preliminary to be interpreted adequately because of the small numbers of patients in each arm.

Ganglioside Vaccines
Univalent vaccines are highly purified and, therefore, are less likely to contain potentially irrelevant material and are also easier to standardize for quality control. On the other hand, single antigens are much less immunogenic and are potentially vulnerable to antigen modulation. Gangliosides were found to be effective targets for active immunotherapy using whole-cell vaccines,[54] or for passive immunotherapy using monoclonal antibodies against various gangliosides.[55,56] Gangliosides are glycosphingolipids that contain a ceramide chain, which is incorporated into the lipid bilayer of the plasma membrane. The carbohydrate moieties are present on the cell surface and are available for antibody recognition.

**GM2 Vaccine**—Using a vaccine composed of the purified ganglioside GM2, Livingston and colleagues demonstrated that sera from immunized patients contained anti-GM2 IgM antibodies, which, through a complement-dependent pathway, lysed GM2-expressing melanoma cells.[22] No IgG antibodies were produced, nor was there a cytotoxic T-lymphocyte response. This finding, coupled with the observation that GM2 is a common antigen on melanoma cells, led to the performance of a phase III trial comparing GM2/BCG vaccine to BCG in 120 patients with AJCC stage III melanoma rendered free of disease by surgery. The vaccine group had a 14% increase in disease-free survival and an 11% increase in overall survival compared to the control group; neither difference was statistically significant.[57] Interestingly, the patients who produced antibody titers against GM2 of 1:40 or more had a significant improvement in both disease-free survival and overall survival.[58]

**Conjugate GM2-KLH-QS21 Vaccine**—To enhance the humoral response to GM2 vaccine, a covalent attachment of GM2 to the carrier protein keyhole limpet hemocyanin (KLH) was developed and was mixed with the adjuvant QS21. This conjugate GM2-KLH-QS21 vaccine induced a prolonged IgG and IgM response that produced complement-mediated lysis of melanoma cells that expressed GM2. This was considered to be an advance over the earlier GM2/BCG vaccine.[59] An intergroup trial comparing high-dose interferon-alfa with the GM2-KLH-QS21 vaccine is currently accruing patients with either AJCC stage III nodal disease or stage III melanoma greater than 4 mm in thickness with negative nodes.

**Other Ganglioside Antigens**—In addition to GM2, other ganglioside antigens, such as GD2, GM3, GD3, and O-acetyl GD3, have shown immunogenicity in melanoma patients[23,60,61]

Novel Approaches to Tumor Vaccines
Since the most important tumor antigens to stimulate an immune response are still unknown, cell-based vaccines continue to be used most commonly in clinical studies. Rapid advances in molecular oncology and tumor immunology have made possible novel approaches that can identify candidate antigens as possible targets for antigen-specific vaccines. Two designs of antigen-specific vaccines are peptide vaccines and DNA vaccines. Vaccines using dendritic cells as antigen carriers also are emerging as innovative forms of active specific immunotherapy.

**Peptide Vaccines**
Antigens that are candidates for optimal response after vaccination continue to be isolated. T-cells isolated from blood or tumor in melanoma patients have been used to identify MHC-restricted peptide antigens, such as the tumor- and melanoma-associated antigens described previously. Vaccines produced using purified peptide preparations of such antigens as MAGE-1,[62] MAGE-3,[63] MART-1/MelanA,[64,65] gp100,[66-68] and tyrosinase[69] are currently under investigation in clinical trials. For example, a phase I trial evaluated a vaccine of a synthetically modified gp100 peptide in patients with metastatic melanoma. This modified peptide enhanced cytotoxic T-lymphocyte activity,
compared to the wild-type gp100 peptide. However, there were no clinical responses unless interleukin-2 (Proleukin) was given in combination with the vaccine.[70] Encouraging preliminary results from a phase I trial that examined a MAGE-3 peptide vaccine in patients with advanced melanoma found some complete responses, but MAGE-3–specific cytotoxic T-lymphocyte responses were not detected, which suggests that these responses were not caused by the peptide vaccine.[71] Although peptide vaccines appear to be promising, much more study is needed to determine whether highly purified peptides will stimulate an adequate immune response. The recent combination of tumor peptide antigens with heat shock proteins, which bind endogenous peptides and can enhance immune response to these peptides, may amplify cytotoxic T-cell responses.[72] Whole proteins may, in fact, be superior to peptides because they contain the antigen itself, which can be enzymatically degraded by antigen presenting cells to produce several peptides that can bind to different MHC class I and II molecules, thereby potentially reducing the impact of MHC restriction. This bypasses the necessity of using a different peptide immunogen for each HLA type.

DNA Vaccines
Nucleic acids can be incorporated as plasmids into viruses, transfected into allogeneic or autologous tumor cells, or left as naked DNA, which can then be used as tumor vaccines. Naked DNA can be incorporated into myocytes of mice after inoculation; such myocytes can then serve as a factory for antigen production and presentation by bone marrow-derived antigen-presenting cells.[73,74] The specific gene encoding for any desired antigen can be produced using standard recombinant technology. The only clinical report of a recombinant DNA viral vaccine was in a small group of patients with advanced cervical cancer. These patients showed evidence of a cytotoxic T-lymphocyte and antibody response to the specific protein encoded by the DNA insert.[75] This strategy is under investigation in melanoma using various epitopes.[76,77]

Dendritic Cell Vaccines
Dendritic cells are extremely potent activators of T-cells. Several methods of vaccination have been actively investigated; these include dendritic cells as carriers loaded with peptides or proteins or dendrites cells fused to whole cancer cells.[78-80] A recent pilot study used dendritic cells pulsed with peptides or lysate and stimulated with a cocktail containing granulocyte-macrophage colony stimulating factor (GM-CSF [Leukine, Prokine ]), interleukin-4 (IL-4), and KLH in patients with AJCC stage IV melanoma. This study demonstrated a delayed-type hypersensitivity response to peptide-pulsed dendritic cells in most patients, and objective partial tumor regression in 5 out of 16 patients.[81] Ongoing research is attempting to determine the antigen composition and dendritic cell loading technique that will most effectively stimulate the host immune system.

Summary
Active specific immunotherapy using vaccines holds promise as a new therapeutic modality for patients with melanoma. Future refinements in the identification of antigens that provoke a maximal immune response, and in the key modulators and enhancers of this response, hopefully will translate into a clinical benefit in terms of producing sustained tumor regression. Phase III randomized, controlled trials are in progress to determine whether particular vaccines that have been in development for many years can result in a true clinical benefit. Novel approaches to vaccine therapy are under active investigation in the laboratory, and preliminary clinical results are promising. Vaccine strategies currently in use range from whole cells or tumor lysates to one or two highly specific purified antigens. More than likely, future developments will combine the advantages of both poles of this spectrum to produce a vaccine with beneficial elements from each design.

References:


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