Active Specific Immunotherapy Phase III Trials for Malignant Melanoma: Systematic Analysis and Critical Appraisal

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The incidence of malignant melanoma is increasing faster than that of any other cancer. In men, it is the fifth most common cancer, accounting for 5% of new cancer cases. In women, it is the sixth most common cancer, with 4% of new cancer cases; only the frequency of lung cancer is rising faster than that of melanoma.[1,2]

Although early stage lesions are curable with adequate surgical resection, postsurgical management of advanced malignant melanoma continues to be a challenge. The 5-year survival rate for patients with local stages of melanoma is 98.3%, compared with 63.8% and 16% for patients with regional or distant metastases, respectively.[2]

There is no effective treatment for metastatic melanoma AJCC stage IV); patients with AJCC stage IIB (T4N0M0) and AJCC stage III (T1–4N1M0) are at high risk of recurrence after definitive surgery. Multiple chemotherapeutic regimens have been used to treat advanced stage melanoma patients, but little effect on overall survival has been found.[3,4]

Although adjuvant therapy with interferon-α-2b was approved by the FDA for patients with stage III melanoma, it is associated with considerable side effects and costs.[5] Similarly, the use of FDA-approved high-dose interleukin (IL)-2 is associated with systemic toxicities.

So it is important to investigate alternative treatment options, including the possibility of inducing an immune response against tumor-associated antigens (TAA) by vaccination, the so-called active specific immunotherapy (ASI).

Tumors express antigens (TAA) are recognized by the immune system as foreign, so they induce a T-cell mediated immune response. The molecular description of the first human TAA was published in 1991 and was a breakthrough in tumor immunology.[6] Since then a large number of these TAA have been described. They are recognized by CD8+ cytolytic T lymphocytes as peptides derived from proteins processed in the cytosol and displayed on the cell surface bound to class I major histocompatibility complex molecules of antigen-presenting cells. But, this immune response frequently is unable to prevent tumor growth because of tumor escape mechanisms, high tumor burden, and weak antigenicity.

Immunotherapy aims at actively enhancing the immune response or at passively delivering immunity. Examples of passive immunotherapy are adoptive cellular therapy, consisting of the transfer of cultured antitumor reactive immune cells, or administration of tumor-specific monoclonal antibodies. Active immunotherapy may be achieved either by specific stimulation, the so-called active specific immunotherapy (ASI), or by nonspecific stimulation of the immune system, eg, by injecting proinflammatory substances such as bacillus Calmette-Guérin or by administration of cytokines and costimulators. ASI enhances the host's immune response by immunization with either killed tumor cells or tumor cell lysates possibly expressing multiple TAA, or with defined tumor antigens. Examples of vaccines using defined tumor antigens are the direct injection of peptides with or without adjuvants or cytokines, the ex vivo loading of antigen-presenting cells (APC) such as dendritic cells with peptides before reinjection, or the use of recombinant virus encoding TAAs and capable of infecting antigen-presenting cells, mimicking the physiologic pathway.

The objective of this review was to critically appraise the current status of ASI for treatment of melanoma. Although there are numerous phase I and II trials and case series, only a few phase III randomized controlled clinical trials were performed. We focused on two endpoints: disease-free survival (DFS) because it is the outcome showing most directly the efficacy of the treatment under investigation, and overall survival (OS) because it is the most important outcome to patients and the outcome best defined and least subject to investigator bias.

Competing Interests Declared: None.

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Abbreviations and Acronyms

ASI = active specific immunotherapy
BCG = bacillus Calmette-Guérin
DFS = disease-free survival
DTIC = dacarbazine
GM2 = ganglioside
GMK = GM2 keyhole limpet hemocyanin
HR = hazard ratio
OS = overall survival
TAA = tumor-associated antigen
VMCL= vaccinia melanoma cell lysate
VMO = vaccinia melanoma oncolysate.

METHODS

Inclusion criteria

Randomized-controlled phase III trials (RCT), published until December 2006, addressing active specific immunotherapy for melanoma patients were included in this review. Phase I and II trials, case series, and retrospective analyses were not considered. Other modalities of immunotherapy, such as passive (use of monoclonal antibodies or adoptive transfer therapy) and nonantigen-specific immunotherapies (cytokines, bacillus Calmette-Guérin, etc) were also excluded.

Search strategy

The review of all relevant articles was based on a Medline search on "melanoma," "immunotherapy, and "phase III," with the limits "clinical trial" and "randomized controlled trial," until December 2006. No time limit was added, so articles published at any date in the past were taken into account, including articles published more than 20 years ago. Additional articles were identified through cross-referencing of the studies retrieved. Ongoing studies were identified by the NIH Website, www.clinicaltrials.gov, using the key words *melanoma*, *immunotherapy*, and *phase III*.

Data analysis

All identified trials were critically appraised for study design, disease-free survival (DFS), and overall survival (OS).

RESULTS

Eight phase III trials were identified.[7-14] All trials provided detailed information about outcomes after ASI. But the design of the studies showed considerable variations. Table 1 summarizes the trials included, and Table 2 provides an overview of the results.

Immunotherapy trials based on whole cell vaccines

Vaccinia virus melanoma oncolysate versus control vaccinia virus

Wallack and colleagues[15-17] performed phase I and II trials to evaluate toxicity and the effective dose of a vaccinia virus-augmented polyvalent melanoma oncolysate vaccine. Based on their promising findings, they randomized 250 stage III melanoma patients (intention-to-treat); 33 of these patients were excluded because they were inadequately operated on, they presented more than one primary melanoma, they had extranodal spread, or they did not have a melanoma. The eligible patients were the remaining 217, who received vaccinia melanoma oncolysate (VMO) or control vaccinia virus.[7]

A polyvalent VMO derived from four allogeneic mela-

Table 1. Summary of Studies Included in this Report

First author,y	Vaccine	Control	n*	Stage†	Followup, mo
Whole cell vaccines					
Wallack, 1998[7]	VMO	V	217 (250)	III	46.3 median
Mitchell, 1997[8]	Melacine	Chemotherapy	106 (140)	IV	–
Sondak, 2002[9]	Melacine	Observation	600 (689)	T3N0M0	67.2 median
Hersey, 2002[10]	VMCL	Observation	675 (700)	IIB/III	96 median
Morton, 2006[11]	Canvaxin	Observation	(1,160)	III	69 median
			(496)	IV	69
Ganglioside vaccines					
Livingston, 1994[12]	GM2/ BCG	BCG	122 (123)	III	63 median
Kirkwood, 2001[13]	GMK	IFNα2b	774 (880)	IIB/III	16 median
Epitope-specific vaccines					
Schadendorf, 2006[14]	DC	DTIC	104 (108)	IV	22.2 median

BCG, bacillus Calmette-Guérin; DC, autologous peptide-pulsed dendritic cells; DTIC, dacarbazine; GM2, ganglioside GM2; GMK, GM2 keyhole limpet hemocyanin-QS-21; IFN, interferon; V, control vaccinia virus; VMCL, vaccinia melanoma cell lysates; VMO, vaccinia melanoma oncolysate.
*Number of eligible patients (intention to treat).
†Stage according to American Joint Committee on Cancer or TNM classification.