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Vaccine therapy of malignant melanoma

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Abstract

Malignant melanoma is a lethal disease for which the only curative therapy of proven benefit is complete surgical resection for early stage disease. Melanoma is a disease that is usually resistant to systemic therapy, with dacarbazine and interleukin-2 being the only 2 United States Food and Drug Administration approved drugs for advanced disease, and interferon alfa-2b the only one approved therapy for adjuvant treatment of high-risk disease. Evidence has shown that melanoma cells can be immunogenic prompting extensive basic and clinical research attempting to develop effective antimelanoma vaccine therapies. In this review, we concentrate on clinical results of vaccine trials in patients with melanoma.

Keywords: Melanoma; Vaccines; Clinical trials

1. Melanoma vaccines

1.1. Introduction

Approximately 55,580 new cases of malignant melanoma are estimated to have been diagnosed in the United States in 2005 [1]; the incidence of this disease has been on the rise [2]. Early detection and complete surgical resection for localized melanoma is the only curative modality proven of benefit with an estimated 10-year survival rate for node-negative disease ranging from 54% to 94% [3]. Unfortunately, patients with melanoma metastatic to the regional lymph nodes (stage III) or distantly (stage IV) have a far worse prognosis with 10-year survivals ranging from 35% to 46% and 6.8% to 14%, respectively [3]. The only 2 drugs approved by the Food and Drug Administration for use in stage IV melanoma treatment are dacarbazine and high-dose interleukin (IL)-2 with modest response rates and

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minimal effects on survival; the only approved therapy for use as an adjuvant in resected high-risk patients is interferon alfa-2b. Improvements in the pharmacologic armamentarium for this lethal disease are thus warranted; one investigative approach has been the use of therapeutic vaccines to try to induce an immune response against the tumor.

Evidence of the immunogenic properties of melanoma was first noticed in anecdotal reports of spontaneous partial and complete regressions of advanced tumors [4]. This was further supported by the observation that immunocompromised individuals tend to have a higher incidence of melanoma suggesting that immune surveillance prevents the development of this disease [5]. The identification of infiltrating T lymphocytes in melanoma specimens and that this finding was of prognostic import [6], as well as the characterization and cloning of melanoma-associated antigens (MAAs) [7,8] supported those clinical observations. All of these findings in addition to in vitro and murine experiments provided the rationale for the development of melanoma vaccines.

Cancer vaccines should be immunogenic to the tumor, but should not cause major immunological toxicities to normal tissues; the vaccine should also be heterogeneous enough to include the antigens present in the specific tumor to be treated. The preparation has to be reproducible, cost effective and safe.

For the purposes of this discussion, based on the antigen and formulation used, one can classify melanomas vaccines into 3 groups: (1) whole-cell–based vaccines, including cell lysates, (2) defined antigens vaccines such as peptides and gangliosides, and (3) dendritic cell vaccines. In addition, there are also plasmid DNA vaccines and recombinant viral vector vaccines developed as a way of producing tumor antigens in vivo while providing prolonged immune exposure and stimulation. This review concentrates on the clinical results of vaccine therapy in patients with melanoma, in-depth reviews of the immunological mechanisms of vaccine therapy in cancer have previously been published [9,10].

2. Whole-cell vaccines

2.1. Autologous whole-cell vaccines

Autologous whole-cell melanoma vaccines are prepared with the patient's tumor cells as the source of the antigens. The potential advantage is that all of the tumor antigens will be present in these vaccines. Unfortunately, there has to be sufficient amount of tumor (usually ≥ 10 g) to obtain enough tissue to prepare the vaccine; thus, these studies tend to select patients with bulkier, more advanced disease. Other disadvantages of this approach are that these vaccines may stimulate regulatory CD4+CD25+ T cells, which by virtue of their immunosuppressive effects may prevent the desired antitumor activity of the vaccine. Immune monitoring as a result would be very difficult. On the other hand, because these vaccines contain self-antigens, they could also potentially induce autoimmune toxicities.

Berd et al. from Thomas Jefferson University conducted clinical studies using autologous intact tumor-cell vaccines in the metastatic and in the adjuvant setting. In a pivotal nonrandomized trial, they immunized 64 patients with metastatic melanoma with irradiated autologous tumor cells mixed with Bacillus Calmette-Guerin (BCG) as adjuvant, and using low-dose cyclophosphamide (300 mg/m^2) 3 days before the immunization, this cycle was