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Vaccination of multiple myeloma: Current strategies and future prospects

Alessandro Allegra *, Giuseppa Penna, Vanessa Innao, Bruna Greve, Valerio Maisano, Sabina Russo, Caterina Musolino

Division of Hematology, Department of General Surgery, Oncology and Pathological Anatomy–University of Messina, Messina, Italy

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Abstract

Tumor immunotherapy holds great promise in controlling multiple myeloma (MM) and may provide an alternative treatment modality to conventional chemotherapy for MM patients. For this reason, a major area of investigation is the development of cancer vaccines to generate myeloma-specific immunity.

Several antigens that are able to induce specific T-cell responses are involved in different critical mechanisms for cell differentiation, inhibition of apoptosis, demethylation and proliferation.

Strategies under development include infusion of vaccine-primed and *ex vivo* expanded/costimulated autologous T cells after high-dose melphalan, genetic engineering of autologous T cells with receptors for myeloma-specific epitopes, administration of dendritic cell/plasma cell fusions and administration expanded marrow-infiltrating lymphocytes. In addition, novel immunomodulatory drugs may synergize with immunotherapies.

The task ahead is to evaluate these approaches in appropriate clinical settings, and to couple them with strategies to overcome mechanisms of immunoparesis as a means to induce more robust clinically significant immune responses.

Keywords: Multiple myeloma; Vaccination; Immunoparesis; Idiotype vaccination; Cell-based vaccines; Cytotoxic T lymphocytes

* *Corresponding author*. Tel.: +39 0902212364; fax: +39 0902213697.
E-mail address: aallegra@unime.it (A. Allegra).

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1. Introduction

Although the discovery of novel biologic agents has improved therapeutic options for patients with multiple myeloma (MM), curative outcomes remain elusive because of the emergence of resistant disease. Actually, the only definitive MM treatment is the allogenic transplantation. However, allogeneic transplantation is associated with significant morbidity and mortality.

Tumor immunotherapy holds great promise in controlling or even eradicating residual diseases and may provide an alternative treatment modality to conventional chemotherapy for MM patients. The unique efficacy of cellular immunotherapy is supported by the observation that allogeneic hematopoietic stem cell transplantation is curative for a subset of patients due to the graft-versus-disease effect mediated by alloreactive lymphocytes [1]. The potency of the graft-versus-myeloma effect is also supported by the disease response following donor lymphocyte infusions.

In fact, there is accumulating evidence that the immune system is not completely tolerant even to established tumors, based on the observation that tumor-infiltrating T cells, when expanded *in vitro* and injected back to lymphopenic patients, have a clinical effect in some patients [2]. Further supporting the notion of ongoing immune responses to tumors, antibodies that block inhibitory molecules on T cells induce long-term remission in a subset of cancer patients [3]. Finally, parameters that indicate immune activation in tumors are associated with improved prognosis [4].

For this reason, a major area of investigation is the development of cancer vaccines to generate myeloma-specific immunity that selectively targets malignant cells while minimizing toxicity to normal tissues. Critical elements required to develop an effective vaccine strategy involve the identification of myeloma-associated antigens, enhancement of antigen presentation, and reversing the immune-suppressive milieu induced by the disease.

1.1. Idiotype vaccination in MM patients

B cell malignancies, including MM, are unique in their expression of immunoglobulin (Ig). The Ig on malignant cells can be distinguished from normal B cells or plasma cells by virtue of specific idiotypic determinants (Id) [5].

In fact, because these malignancies are monoclonal, all the cells of a given tumor express or secrete identical Ig. However, these antigens are ordinarily not recognized as foreign by the body's immune system. Nevertheless, the Id has been exploited as a target for active immunotherapy.

Eisen et al. demonstrated that immunization with a monoclonal Ig, myeloma protein M315, induced anti-Id antibodies in syngeneic BALB/c mice [6]. This finding indicated that Ig V regions can be autoimmunogenic, as demonstrated by Rodkey [7].

However, immunogenicity of various monoclonal Ig differed. In particular, an abundant Ig with germline-encoded V regions (T15) failed to induce anti-Id antibodies, presumably due to self-tolerance [8]. Hence, somatic mutations and/or V(D)J junctional diversity appear to be required for sufficient "foreignness" of Id to be immunogenic in an autologous setting.

The first generation of Id vaccines consisted of purified Id or Id protein conjugated to an immunogenic carrier protein. Vaccination with these vaccines conferred protection against tumor challenge in a number of lymphoma and myeloma animal models [9,10]. Based on these preclinical results, immunization with autologous Id has been initiated in clinical trials to control residual disease in B cell lymphoma and multiple myeloma [11–13].

Interestingly, patients with monoclonal gammopathy of undetermined significance (MGUS), which is a pre-myeloma clonal plasma cell disorder, often exhibit a humoral response against autologous bone marrow plasma cells [14].

However, Id-protein alone is only weakly immunogenic. The low immunogenicity of Id is probably related to B and T tolerance, the levels of which may vary with various individual Ids. Nevertheless, its immunogenicity can be potentiated by conjugation with a strong immunogen such as keyhole limpet hemocyanine [15].

In fact, recent studies have shown that although Id proteins were efficient in protecting mice from subsequent tumor challenge, the antigen by itself is not enough to promote the differentiation of naïve T cells into effector cells [16]. Tumor-associated antigens (TAA), which are poorly immunogenic, elicit anergic or regulatory T cells, when administered alone without appropriate immunostimulatory molecules.

Indeed, in many instances tumors can escape the host immune response. Many mechanisms of tumor escape have been proposed: low expression of molecules on tumor cells involved in tumor target cell recognition; absence of co-stimulation leading to tolerization of T cells; soluble factors secreted by tumor cells inhibiting T cell response and regulatory T cells, and stromal cells may impair immune-cell responses to tumors. Furthermore, tumors can release soluble molecules such as HLA-I (sHLA-I). This, in turn, reduces T cell-mediated immune response and induces apoptosis of cytolytic effector cells such as natural killer and CD8(+) T lymphocytes through the engagement of HLA-I receptors such as CD8 and/or activating isoforms of the inhibitory receptor superfamily. The release of soluble ligand for activating receptors may impair activation, effector cell-mediated recognition, and cytolysis of tumor cells.

Thus, immunological adjuvant is one of the important strategies to enhance the desired immune responses to weak antigens [17]. Thus far, many investigators have examined vaccination with Id protein in combination with immunological adjuvants, such as granulocyte–monocyte colony-stimulating factor (GM-CSF), interleukin (IL)-12 and aluminum, for the treatment of patients with MM as well as other B-cell malignancies [12,18–20].

Hong et al. explored and compared the effects of Id protein-based immunotherapy in combination with