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Short Report

A Clinical Study of a Cell-Based MAGE-A3 Active Immunotherapy in Advanced Melanoma Patients

Vincenzo Russo[1], Francesca Lunghi[2], Raffaella Fontana[1] and Marco Bregni[3] ✉

1. Cancer Gene Therapy Unit, San Raffaele Scientific Institute, via Olgettina 60, 20132, Milan, Italy;
2. Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, via Olgettina 60, 20132, Milan, Italy;
3. Strategic Program in Oncology, San Raffaele Scientific Institute, via Olgettina 60, 20132, Milan, Italy.

✉ Corresponding author: Marco Bregni, M.D., Department of Hematology, San Raffaele Scientific Institute, via Olgettina 60, 20132, Milan, Italy. Phone 39-02-26434409 Fax 39-02-26434760 e-mail marco.bregni@hsr.it

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Abstract

In this bi-institutional study, twenty-three stage IIIC-IV MAGE-A3$^+$ melanoma patients were vaccinated with M3TK-GML biweekly at three dose levels, with a subsequent phase of vaccinations at the maximum dose level. Anti-MAGE-A3 and anti-TK T cells were assessed by *in vitro* assay and delayed-type hypersensitivity skin testing.

Key words: MAGE-A3, Melanoma, Immunotherapy

In-vivo targeting of dendritic cells (DC) has been shown to confer strong and protective cytotoxic T lymphocyte (CTL)–based immunity in tumor murine models. Our group has recently demonstrated in preclinical models[1] that the infusion of genetically modified lymphocytes (GMLs) expressing the self/tumor antigen TRP-2 is able to elicit functional TRP-2–specific effectors with antitumor activity by targeting DCs in vivo. The mechanism responsible for the induction of such an immune response is the cross-presentation of the antigen mediated by the CD11c$^+$CD8α$^+$ DC subset. Furthermore, we demonstrated in vivo and in vitro that DCs had undergone activation upon phagocytosis of genetically modified lymphocytes, a process mediated by a cell-to-cell contact mechanism independent of CD40 triggering. Targeting and activation of secondary lymphoid organ–resident DCs endowed antigen-specific T cells with full effector functions, which ultimately increased tumor growth control and animal survival in a therapeutic tumor setting. This original strategy was exploited for active immunotherapy of patients with advanced melanoma, a tumor with known susceptibility to immune control[2]. Autologous lymphocytes collected by apheresis were transduced with retroviral supernatant (Sup PG13LM3TN #21, MolMed S.p.A.) containing LM3TN vector, a construct that expresses the genes MAGE-A3 and the HSV-TKneo fusion protein (TN) (*i.e.* M3TN vector). Transgene-expressing cells were G418 selected and expanded in GMP conditions, and subsequently frozen. We have already reported[3] vaccine- and tumor-specific immune responses of 10 melanoma patients treated with autologous GMLs expressing the cancer germline gene *MAGE-A3*. Three of 10 patients treated with MAGE-A3–GML showed an increase of circulating anti–MAGE-A3 T cells, and developed skin delayed-type hypersensitivity to MAGE-A3. Interestingly, in 2 of these patients, with progressive and measurable tumors at study entry, anti–MAGE-A3 T cells were detected not only in the blood but also within tumors resected after vaccination. These results suggest that the infusion of MAGE-A3–GML elicits antitumor T cells, which are

capable of trafficking to inflamed tissues and of infiltrating tumors. We are now analyzing the clinical results of this strategy on a larger group of patients to evaluate its clinical efficacy. In this bi-institutional study, twenty-three stage IIIC-IV MAGE-A3$^+$ melanoma patients were vaccinated with M3TK-GML biweekly at three dose levels, with a subsequent phase of vaccinations at the maximum dose level. Anti-MAGE-A3 and anti-TK T cells were assessed by *in vitro* assay and delayed-type hypersensitivity skin testing. Patients with measurable disease (19) were evaluated for objective clinical response by Response Evaluation Criteria in Solid Tumors. All patients were pretreated with surgery, and the majority with chemotherapy and/or immunotherapy. Eight patients had skin/subcutaneous disease only, and the remainder had visceral disease. LDH levels were elevated in 8 (36%) of the patients. Clinical responses, progression-free survival and overall survival will be assessed and correlated with the generation of antitumor immune response.

Conflict of Interest

The authors have declared that no conflict of interest exists.

References

1. Russo V, Cipponi A, Raccosta L, et al. Lymphocytes genetically modified to express tumor antigens target DCs in vivo and induce antitumor immunity. J Clin Invest 2007;117:3087-3096.
2. Eggermont AM, Schadendorf D. Melanoma and immunotherapy. Hematol Oncol Clin North Am. 2009;23:547-564.
3. Fontana R, Bregni M, Cipponi A, et al. Peripheral blood lymphocytes genetically modified to express the self/tumor antigen MAGE-A3 induce antitumor immune responses in cancer patients. Blood 2009;113:1651-1660.