Adoptive transfer of antigen-specific CD4$^+$ T cells in the treatment of metastatic melanoma

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The adoptive transfer of antigen-specific CD4$^+$ cells is a feasible treatment for cancer and provides critical insight into immune mechanisms involved in durable clinical responses.

Summary

Clinical investigations of adoptive therapy in solid tumours have primarily focused on CD8$^+$ cells. A study by **Hunder et al**. is the first to demonstrate the significance of antigen-specific CD4$^+$ T cells (**Treatment of metastatic melanoma with autologous CD4$^+$T cells against NY-ESO-1**. *N Engl J Med* 358:2698–2703). An *in-vitro* method was used to treat a patient with metastatic melanoma using autologous CD4$^+$ cells against NY-ESO-1 (cancer and/or testis antigen 1). The successful adoptive transfer of antigen-specific CD4$^+$ cells to a patient with metastatic melanoma is not only an important technical accomplishment but also provides increased understanding of tumour immunity. This report demonstrates an impressive persistence of adoptively transferred cells together with durability of clinical response. CD4$^+$ T cells that target a particular antigen can augment T-cell responses to other tumour-associated targets. These observations underline the importance of ongoing research for effective, non-toxic immune therapies for cancer.

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Most investigations in adoptive therapy have focused on CD8$^+$ cells, because these cells have the direct effector function of cell killing. The importance of CD4$^+$ cells, and their role in helping to elicit an effective immune response, has not been well studied in patients with cancer. The antigen, NY-ESO-1 (cancer and/or testis antigen 1), is a member of the cancer and/or testis antigen family, which has high expression in the testis and placenta, but not in other normal adult tissues. *CTAG1B* (cancer and/or testis antigen 1B), *MAGEA* (melanoma antigen family A), *BAGE* (B melanoma antigen family), and *GAGE* (G antigen) are frequently expressed in a number of malignancies including melanoma. Humoral and cellular immune responses to NY-ESO-1 have been extensively analysed in patients with cancer and this antigen is an ideal candidate for a potential therapeutic strategy.

Some patients have demonstrated measurable antitumour immune recognition. The best method to augment an immune response against a particular tumour antigen and thus achieve a meaningful clinical benefit is a hotly debated issue. One approach to augment this antitumour immune response is the direct infusion of autologous, antigen-specific T cells that have been isolated from patients and expanded *in vitro*. For patients with metastatic

melanoma, highly specific and potent T cells have been successfully generated from either endogenous, tumour-infiltrating lymphocytes or by the use of antigen-receptor gene transduction to enforce and initiate antigen recognition.[2–4] Adoptive transfer of autologous $CD8^+$ cultures to patients who have been depleted of lymphocytes by high-dose chemotherapy is a promising methodology. With subsequent administration of high-dose interleukin 2, these adoptively transferred cells can be expanded *in vivo* and targeted to pre-existing tumour sites, which leads to a durable clinical response. Most studies have used melanocytic antigens such as MART-1 (melanoma antigen recognised by T cells 1, also named Melan-A), many of which are transcriptional targets of the melanoma oncogene *MITF* (microphthalmia-associated transcription factor).[5] Autologous lymphocyte infusions have produced objective tumour responses in approximately 50% of patients with melanoma for whom cells for adoptive transfer were successfully generated.[6] Current limitations of adoptive transfer include the restricted persistence of adoptively transferred cells in the recipient, suboptimal homing of cells to tumour deposits, and ensuring the purity of the antigen-specific $CD8^+$ T cell population infused into patients.

Hunder et al.[1] demonstrate the feasibility of *ex-vivo* isolation and expansion of antigen-specific $CD4^+$ clones with successful adoptive transfer into a patient with advanced melanoma. The study complements previous research by first tackling an important feasibility issue: the ability to produce an autologous, clinically pure, antigen-specific $CD4^+$ cellular product. The authors should be commended for the labour-intensive process used to generate the adoptively transferred cells, as it involved cloning $CD4^+$ lymphocytes. The potency and persistence of transferred cells are crucially important and have been major concerns in the feasibility of adoptive therapy for the treatment of cancer. The 52-year-old patient presented in this report exhibited an extended, beneficial, clinical response (the patient was in remission for 22 months) and this therapy warrants further investigation. The patient was unresponsive to prior high-dose interferon and interleukin 2.

The study by Hunder and co-authors highlights the biologic importance of $CD4^+$ T cells as agents for cancer therapy. In patients with chronic myelogenous leukaemia who relapse after allogeneic bone marrow transplant, infusions of $CD4^+$ cells are known to produce an effect similar to the 'graft-versus-leukaemia' response. $CD4^+$ cells obtained from the donor of the allogeneic bone marrow transplant can lead to further clinical responses and remissions. Augmented T-cell responses to melanoma-associated antigens occurred despite the lack of allograft recognition opportunities, which indicates an important mechanism of action for adoptively transferred $CD4^+$ T cells.[1] The immune helper function of $CD4^+$ cells leads to expansion of a heterogeneous immune population of effector cells that respond to multiple tumour antigens. Similar phenomena, including for example epitope spreading, have been previously reported with anti-cancer immunotherapy.[7] The role of infused $CD4^+$ T cells in evoking immune responses to tumour-specific antigens is of great importance, both scientifically and clinically.

These technical and scientific accomplishments should not go unnoticed in the broader field of anticancer immunotherapy. Immunotherapies for cancer have undergone decades of investigation, with research into the development of vaccines derived from autologous or allogeneic tumours, peptide vaccines, cytokines and immune adjuvants. Advances in our understanding of immune mechanisms have consolidated such efforts. Immune checkpoints determine the type and potency of antigen-specific immune responses in the autologous setting, and an improved understanding of immune regulatory cells provides further therapeutic opportunities. The best-developed clinical example is the blockade of cytotoxic T lymphocyte antigen 4 by human monoclonal antibodies. In clinical trials, expansion of antitumour immune cells, lymphocyte infiltration of tumours, tumour destruction and clinical benefit have been demonstrated in some patients. However, this therapy has been associated with an increased risk of autoimmune phenomena, such as diarrhoea due to bowel inflammation. $CD4^+$ T-cell adoptive-transfer therapy could offer great therapeutic promise, either alone or in combination with other strategies, for successful triggering of tumour immunity. This strategy should be investigated further in the hope that effective, nontoxic therapies can be developed for patients with cancer.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

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