

Human cancer immunotherapy: progress and problems

Steven A. Rosenberg

National Cancer Institute, Bethesda, MD

Recent studies have shown that immunotherapeutic approaches can reproducibly mediate the regression of large metastatic cancers in patients (1, 2).

The identification of the molecular nature of cancer associated antigens has enabled the evaluation of active immunization (cancer vaccine) approaches to the treatment of humans with metastatic disease. We recently evaluated our results of the treatment of 440 patients with metastatic cancer treated with 541 cancer vaccines in the Surgery Branch, NCI (3). A variety of approaches were explored including the use of immunogenic peptides, recombinant viruses, naked DNA and peptide-pulsed dendritic cells. Despite the ability to generate high levels of anti-tumor lymphocyte precursors, especially using anchor-modified peptides, our objective response rate (using WHO or RECIST criteria) was only 2.6%. An analysis of 35 published reports that included 765 patients treated with a variety of cancer vaccines revealed an objective response rate of 3.8%. Thus, although cancer vaccines hold considerable promise for the development of effective cancer immunotherapy, modifications of current approaches are desperately needed.

We recently completed a study of 128 patients treated with peptide vaccines over the course of 48 weeks in the adjuvant setting. This prolonged immunization generated antigen reactive precursors at levels up to 20% in all CD8+ cells. It is not known, however, whether these high levels can prevent cancer recurrence in the adjuvant setting. A study in 56 patients with metastatic melanoma who received peptide immunization in conjunction with the administration of anti-CTLA4 monoclonal antibody (MDX-010) resulted in an overall objective regression rate of 13% including metastases that regressed in the lung, liver, brain, lymph nodes and subcutaneous sites (4). Autoimmune toxicity was seen that highly correlated with cancer regression ($P = 0.008$).

We recently completed a study in 35 patients with metastatic melanoma refractory to treatment with IL-2 who underwent lymphodepleting conditioning with cytophosphamide and fludarabine followed by the infusion of autologous, tumor reactive, expanded tumor infiltrating lymphocytes (TIL) and IL-2 (1, 2). Eighteen of 35 patients (51%) experienced an objective clinical response including regression of metastases in lung, liver, lymph nodes, brain and subcutaneous sites. Tumor regression was highly correlated with the persistence of the administered cells ($P = 0.001$) which sometime reached as high as 80% of all circulating CD8+ cells. Thus cell transfer approaches can be highly effective for the treatment of patients with metastatic melanoma. We are currently conducting studies of intensified lymphodepletion using whole body irradiation prior to cell transfer as well as studies of the genetic modification of peripheral lymphocytes with retroviral vectors encoding T cell receptors as well as the modification of TIL with genes encoding interleukin-2.

References

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