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Getting Personal with Melanoma

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Abstract

Long term follow up of patients with metastatic melanoma who received adoptive immunotherapy with autologous tumor infiltrating lymphocytes shows that patients who attained complete remission have durable responses with 19 of 20 such patients remaining in remission for greater than 3 t greater than 7 years.

In this issue of *Clinical Cancer Research*, Rosenberg et al provide long term follow-up data on 93 patients with metastatic melanoma who received “personalized therapy” for their disease, which took the form of infusions of autologous tumor-infiltrating lymphocytes (TILs) after lymphodepletion. They describe three sequential clinical trials in which they progressively increased the intensity of the lymphodepletion regimen by addition of higher doses of total body irradiation to a chemotherapy backbone of fludarabine and cyclophosphamide.(1) The initial reports of outcomes on these studies have been previously published but this article now describes their results at a median follow-up of 62 months. The increasing intensity of lymphodepletion was associated with increasing objective and complete response rates (from 49% to 72% and 12% to 40% respectively). Of particular note of 19 of the 20 patients attaining complete remission have remained in remission for >3 to >7 years.(1) This long term CR rate is particularly impressive given that the trials targeted high risk populations in which many patients had been heavily pretreated and had visceral metastases at the time of T cell infusion.

The above results show that adoptive T cell immunotherapy can produce durable disease control, an effect also observed in other studies of T cell immunotherapy, including donor lymphocyte infusion to treat relapse after allogeneic hemopoietic stem cell transplant,(2) infusion of cytotoxic T lymphocytes targeting lymphoma or nasopharyngeal cancer (3-6) and in one patient with melanoma who received autologous CD4+ T-cell clones with specificity for the melanoma-associated antigen NY-ESO-1.(7) In the TIL studies reported here, factors associated with objective response included longer telomeres of the infused cells, the number of CD8+ CD27+ cells infused and the persistence of the infused cells in the circulation at one month.(1) In this report data was not provided on longer term persistence of the infused cells, but studies using genetically modified T cells have shown persistence for up to a decade (3;8) which may contribute to long term disease control.

Until March 2011, Dacarbazine and Interleukin-2 were the only two agents currently approved for the therapy of melanoma by the Food and Drug Administration (FDA) but in the last year two significant studies of new agents targeting this disease have been published and one has resulted in approval of another agent. PLX4032, an inhibitor of mutated BRAF (9) has produced an impressive response rate with 26 of the 32 patients treated at the recommended phase 2 dose having an objective response (81%) although only 2 of these

patients had a complete response. These responses, however, were not often complete (2/26 CR) or completely durable, although the median duration of progression-free survival was >7 months and was not reached at the time the data was submitted for publication. Ipilimumab, a monoclonal antibody against the inhibitory lymphocyte receptor CTLA-4 that down-regulates pathways of T-cell activation, also has activity in melanoma. Patients with metastatic melanoma were randomly assigned to receive Ipilimumab alone or in combination with a glycoprotein 100 peptide vaccine or the vaccine alone.(10) There was an objective response rate of 7% in the 540 patients who received one of the two Ipilimumab containing regimens but responses to ipilimumab continued to improve for several months and a significant proportion of these patients maintained an objective immune response for over 2 years.(10) Moreover, improvements in both overall survival and progression-free survival were seen in the patients who received anti-CTLA-4 therapy, compared with the control patients who received the vaccine only. The median overall survival was 10.0 months in patients who received ipilimumab plus the vaccine and 10.1 months in those who received ipilimumab alone, compared to 6.4 months in patients who only received the vaccine. Based on these results the FDA approved the use of ipilimumab to treat patients with late-stage (metastatic) melanoma on March 25th 2011.

The observation that sustained complete responses can be achieved both by infusion of TILs and administration of Ipilimumab supports the contention that immune modulation can effectively control disease in at least a subset of patients with advanced melanoma. Therapy with TILs is not an option for all patients with metastatic melanoma as manufacture of this product requires both that a suitably sized tumor lesion is accessible so that it can be resected to obtain TIL and that a cell product can be generated by ex vivo culture and expansion – a requirement currently met by around 45% of patients with metastatic melanoma.(1) The manufacturing protocols for TIL generation are exportable to other institutions(11) and have been facilitated by recent changes in manufacturing that incorporate newer cytokine and co-stimulatory molecule technology in improved bioreactors. A recent white paper proposed a randomized multicenter study of TIL therapy. For this to be feasible, investigators will need to develop a consensus about the optimal lymphodepletion regimen and control group, define manufacturing processes and decide on the post infusion cytokine support (11). Given the sustained complete responses described in this report, development and design of such a study should be a priority.

The long term benefit of TIL infusions described in this report also justifies exploration of other T cell therapy approaches in patients with metastatic melanoma. Figure 1 summarizes T cell strategies that are currently undergoing clinical testing. Several investigators have described methodology for generation of CD8+ or CD4+ antigen specific T cell clones by stimulation of responding T cells with antigen presenting cells pulsed with peptides derived from tumor antigens expressed by melanoma cells. (7) An alternative strategy is to genetically modify non-specifically activated T cells with artificial receptors specific for tumor antigens. The NCI group have identified TCRs that are highly reactive to melanoma/ melanocyte antigens from screens in immunized transgenic mice and from cloning TIL lines and undertaken clinical trials where these TCRs are transferred to activated peripheral blood lymphocytes.(8) Objective response rates of 19-30% have been reported.(8) An alternative strategy is to transduce T cells with chimeric antigen receptors (CARs) consisting of an antigen binding exodomain and a T cell signaling endodomain so that the antigen specificity of an antibody and the cytotoxic properties of a T cell are combined in a single fusion molecule. Preclinical studies have evaluated the non-protein tumor antigen disialoganglioside 2 (GD2) since it is expressed by the majority of melanoma cells and cannot be targeted by the conventional TCR.(12) For individuals in whom TIL manufacture fails or TIL infusions do not produce clinical benefit, adoptive immunotherapy with such other T cell products may be considered.

All the above adoptive T cell therapies may be further improved by combination with antibodies that targeting downregulators of T cell activation such as CTLA-4 or block other negative regulators of immune function such as PD1 or by blocking immunosuppressive cells and cytokines in the tumor microenvironment. Longer term, the optimal personalized therapy for melanoma may be to combine therapies that act by different mechanisms. For example it may be possible to combine T cell immunotherapy approaches directed to melanoma antigens with targeted small molecules that inhibit aberrantly activated pathways in the individual's tumor.

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A

B

Figure 1.

Figure 1 shows T cell therapies targeting melanoma. Tumor may be harvested and tumor infiltrating lymphocytes harvested and cultured for subsequent infusion to the patient (1A). Peripheral blood mononuclear cells may be genetically modified with a chimeric antigen receptor (shown) or a T cell receptors specific for an antigen expressed by tumor cells (1B). Peripheral blood mononuclear cells may be stimulated with peptides derived from a tumor antigen expressed on antigen presenting cells to generate T cell clones which recognize tumor antigens (1C)