Phase I study of infusion of HER2/neu (HER2) specific T cells in patients with advanced-stage HER2 overexpressing cancers who have received a HER2 vaccine

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Background

- HER2/neu (also known as ErB-2) is a protein member of the ErbB protein family more commonly referred to as the epidermal growth factor receptor family.
- It is a protein generally conferring a worse prognosis in cancers where it is overexpressed: breast, ovarian, gastric, endometrial carcinoma.
- Human tumors are known to be immunogenic. The HER2/neu oncogenic protein is a tumor antigen. Antibody, helper T-cell, and cytotoxic T-cell immunity has been observed in patients with malignancies and the HER2/neu protein represents an excellent target for therapies, proven with agents such as trastuzumab.
- Potential approaches include vaccination strategies in which tumor-associated antigens (TAAs) are presented to induce antigen-specific T-cell responses in vivo and adoptive cell transfer strategies, in which TAA-reactive T cells are generated ex vivo and then infused into the patient to increase the number of tumor-reactive in vivo effector cells.
- The proof of principle for adoptive T-cell therapy was demonstrated in the use of this therapy to control relapse in hematologic diseases and viral infections after allogeneic bone marrow transplantation.
- Tumors have been successfully eradicated in murine models with adoptively transferred T cells but the translation into readily available clinical therapies has been more difficult. However, adoptive T-cell therapy has shown promise in the treatment of advanced-stage melanoma.
- The authors have previously demonstrated that the expansion of HER2-specific T cells from peripheral blood mononuclear cells (PBMC) can be greatly facilitated by vaccine-priming.
- In this study, the authors evaluated the safety and clinical efficacy of infusion of HER2-specific T cells in patients with advanced HER2 overexpressing cancers.

Materials and Methods

- Tumor-specific T cells can be efficiently expanded from the peripheral blood ex vivo following in vivo vaccine priming. This approach provides an effective method to generate tumor-specific polyclonal T cells for therapeutic use that could be applied to cancer patients with any tumor type.
● 10 patients were selected for treatment and enrolled for this therapy in a phase I dose escalation study, all of whom had progressive HER2+ metastatic breast and ovarian cancer, not considered curable by conventional therapies.

● Patient's had to have progressive HER2/neu overexpressing disease that was treatment refractory and must have been pre-immunized with a HER2-specific vaccine.

● Inclusion criteria also included: measurable soft tissue disease, ability to undergo leukapheresis, and patients had to have a normal left ventricular ejection fraction.

● Cyclophosphamide or denileukin diftitox was administrated before the first dose of T cells.

● In the study, a total of three escalating doses of T cells were administered at 10-day intervals.

● Response was assessed radiographically at day 40.

Results

● To date, 5 of 10 subjects have been enrolled.

● T cells were expanded with HER2-specific class II restricted peptides.

● After in vitro expansion, cell products were >95% CD3+ with an average of 35% CD4+ and 60% CD8+ T cells. The maximal doses infused were 1x10⁹ - 41x10⁹ cells (median 10x10⁹).

● Subjects tolerated the infusions well with the primary toxicity being related to the conditioning agent (cyclophosphamide or denileukin diftitox). Overall, 111 adverse events were reported, 90% of which were grade 1 or 2 in nature.

● Of the 5 patients treated, 4 had breast cancer and 1 had ovarian cancer. An objective tumor response was observed in 2 of the 5 patients treated and one other patient had stable disease following treatment.

● In patients with tumor regression, the magnitude of HER2-specific T cells in the infused product was 8-fold higher than that in patients without clinical responses.

● The total number of HER2-specific T cells infused was 43-fold higher in responding patients than in non-responding patients. Moreover, HER2-specific CD4+ and CD8+ T cells persisted over a year and were even augmented in magnitude post-infusion in responding patients.

Author’s Conclusions

● This study demonstrates that HER2/neu-specific polyclonal T cells are readily expressed and the therapy is well tolerated with little grade 3 toxicity observed in treated patients.

● 3/5 of the treated patients had improvement in disease burden or stable disease.

● The clinical response strongly associated with the magnitude and persistence of the HER2-specific CD4+ and CD8+ T cells.

● Bottom Line: Adoptive transfer of autologous HER2-specific polyclonal T cells generated from PBMC after vaccine-priming is well tolerated and demonstrates evidence of some clinical efficacy in patients with advanced-stage HER2+ cancers.

Clinical/Scientific Implications

● Adoptive T-cell therapy is a promising strategy for the treatment of patients with established tumors but is often limited to specific cancers where tumor-infiltrating lymphocytes, the source of T cells for ex vivo culture, can be obtained.

● The data demonstrate radiographic responses correlating to reductions in visceral disease in 2/5 treated patients and clinical response was strongly associated with the magnitude and persistence of T-cells.

● The data are impressive but obviously limited by the very small number of treated patients.
● It is interesting to note that a mixed population of T-cells with strong clonality was demonstrated to survive for extended periods of time in the circulation of patients treated with cancer vaccines without lymphoid depletion or interleukin-2 administration.

● The next steps should include expanding number of treated patients, use of lymphoid depletion and testing effects of reversal of costimulatory blockade.