

Treatment of High Risk Acute Leukemia with CD40 Ligand and IL-2 Gene Modified Autologous Bone Marrow Fibroblasts And Tumor Cells

1. Description

Based on previous pre-clinical and clinical studies showing that the immune system can be stimulated to mount an in vivo anti-tumor response, we propose to study the safety and efficacy of a tumor vaccine for acute leukemia in a Phase I clinical trial. We will use two immunostimulatory agents, interleukin-2 and CD40 Ligand in combination. In previous clinical studies in neuroblastoma, melanoma and renal cell carcinoma, interleukin-2 transduction of tumor cells has been shown to generate an effective anti-tumor response and to be safe, whilst pre-clinical studies have shown that transgenic expression of CD40 Ligand enhances these effects. The benefits can be produced by transducing the tumor cells directly or by co-injecting transduced carrier cells, such as fibroblasts, together with unmodified autologous tumor cells. We propose using adenoviral vectors encoding the human CD40 Ligand gene and the human interleukin-2 gene to transduce cultured fibroblasts from each patient's bone marrow. Leukemic blasts isolated from each patient at relapse will be frozen and stored and injected with the transduced fibroblasts, in a dose escalation study. All cells will be irradiated prior to injection. Fibroblasts will be > 20% CD40+ and secreting >150 pg of interleukin-2/10⁶ cells/24 hours. Hence, this trial will assess the safety of the dose escalation of recombinant CD40 Ligand autologous bone marrow fibroblasts injected with a fixed dose of recombinant IL-2 bone marrow fibroblasts and a fixed dose of autologous leukemia blasts.

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2. Objectives

- 1) To determine the safety of four to six subcutaneous injections of autologous tumor cells admixed with autologous gene modified fibroblasts. These fibroblasts will be expressing the human CD40 Ligand and interleukin-2 genes following adenoviral vector transduction.
- 2) To determine whether MHC restricted or unrestricted anti-tumor immune responses are induced by subcutaneous injection of this cellular combination and to determine the cell dose required to produce these effects.
- 3) To obtain preliminary data on the anti-leukemic effects of this treatment regimen.

3. Treatment Schedule

Relapsed or refractory patients who have entered a state of complete or partial cytological remission (< 20% blasts infiltrating the bone marrow) will receive up to six injections of their gene modified CD40 Ligand and IL-2 bone marrow fibroblasts and leukemic blasts separated by 1-2 weeks in an immunological treatment window, that is, in the absence of concurrent therapy. Patients will receive a fixed dose of IL-2 secreting fibroblasts (2×10^7 per injection) and of leukemic blasts (2×10^7 per injection) throughout the treatment protocol. The first level of the study using the initial three patients will be a safety evaluation of IL-2 fibroblasts with leukemic blasts. Escalating number of CD40 Ligand fibroblasts will then be added to subsequent patient groups if the IL-2 fibroblasts alone prove to be safe. Injections 1-4 will be given at one to two weekly intervals and if

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there is evidence of an objective response without excessive toxicity, the patient may receive up to two additional subcutaneous injections. Injection volumes will not exceed 1 ml. After a 3-4 week rest, patients will be completely re-evaluated for evidence of toxicity and response.

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