Interleukin-2 After T-Cell–Depleted Allogeneic Bone Marrow Transplantation

To the Editor:

The main complication of T-cell–depleted allogeneic bone marrow transplantation (TCD-BMT) is the increased incidence of leukemic relapses.[1,2] In a recent issue of *Blood,* Soiffer et al[3] report on the use of interleukin-2 (IL-2) after TCD-BMT as a strategy for compensating the loss of graft-versus-leukemia effect associated with the removal of alloreactive T cells. In line with previous reports from the same group,[4] in that study an increase in both the number of natural killer (NK) cells and the cytotoxic activity was observed, with these results suggesting that long-term intravenous therapy with IL-2 after TCD-BMT might decrease the leukemia relapse rate.[3] Nevertheless, one of the problems of that treatment is the need to maintain a central venous catheter for a prolonged period of time in an outpatient setting, which is not only uncomfortable and costly but also increases the risk of infection. As suggested by Soiffier et al,[3] the effectiveness of IL-2 administered subcutaneously is, therefore, worthy of investigating.

We have analyzed the effect of IL-2 administered subcutaneously in eight patients (3 men and 5 women; median age, 43 years; range, 34 to 51 years) who underwent TCD-BMT. Chronic myelogenous leukemia in first chronic phase was the most common indication for BMT (n = 6), followed by acute myeloid leukemia (n = 2). The method for TCD was counterflow centrifugation in six patients and monoclonal antibodies plus rabbit complement in two (number of T cells/kg administered: 0.3 to 2×10^6). Post-BMT graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine alone. Human recombinant IL-2 (Proleukin; EuroCetus B.V., The Netherlands) was administered on an outpatient basis by subcutaneous injection 4 days a week to the eight patients. The starting IL-2 dose ranged from 0.5 and 2×10^6 IU/m^2/day, with weekly scalation of the dose (0.5 to 1×10^6 IU/m^2). Planned duration of the treatment was 3 to 6 months. Weekly clinical and analytical controls of each patient were performed, including immunophenotypic studies: CD3, CD16, CD56, CD4, CD8, CD19, CD25, and T-cell receptor α/β and γ/δ. The median interval between BMT and the beginning of IL-2 therapy was 6 months (range, 3 to 20 months). The treatment was discontinued in four patients because of leukemic relapse (1 case), immune thrombocytopenia (1 case), or cutaneous GVHD (2 cases). The maximum dose of IL-2 administered was of 2.5 to 6×10^6 IU/m^2/d. The most common adverse effects observed were fever, fatigue, and nausea (n = 7) and inflammatory nodules at the injection site (n = 8). Significant weight loss was noted in three patients. No infections were documented. GVHD was confirmed by skin biopsy in two patients, after 2 and 5 weeks of starting IL-2 and 4.5 and 6 months after TCD-BMT, respectively. In both patients, GVHD was limited to the skin. Upon IL-2 discontinuation and treatment with prednisone, one of these two patients responded quickly, whereas the other one was resistant and eventually died from sepsis with generalized cutaneous GVHD. At the end of IL-2 treatment, immunophenotypic analysis of peripheral blood showed a 2.5-fold (range, 2-fold to 6-fold) mean increase in the percentage of circulating $CD56^+/CD3^-$ cells in six of the patients and no increase in the other two. No significant changes in CD3, CD25, and T-cell receptor expression were observed.

In summary, in this short series of patients, subcutaneous administration of IL-2 was associated with mild adverse effects in the majority of the cases. This route of administration allows patients to easily perform their normal activities and is associated with a minimum risk of infection. However, in contrast with the findings by Soiffer et al,[3,4] in our patients the effect of IL-2 on the number of NK cells was only moderate. This difference could be attributed to the route of administration or, alternatively, to the longer period elapsed between TCD-BMT and IL-2 treatment, because it appears that the longer the interval between BMT and IL-2 therapy, the lower the NK cell response.[3] Further studies should determine the optimal dose, best treatment schedule, and efficacy of IL-2 in TCD-BMT.

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