CORRESPONDENCE

LONG-TERM FOLLOW-UP OF A RANDOMIZED TRIAL OF GRAFT-VERSUS-HOST DISEASE PREVENTION BY METHOTREXATE/CYCLOSPORINE VERSUS METHOTREXATE ALONE IN PATIENTS GIVEN MARROW GRAFTS FOR SEVERE APLASTIC ANEMIA

To the Editor:

In 1986, we described a prospective randomized trial in which methotrexate/cyclosporine was compared with methotrexate alone for preventing acute graft-versus-host disease (GVHD) in patients given HLA-identical marrow transplants for treatment of severe aplastic anemia.[1] We observed 18% acute GVHD among 22 patients given methotrexate/cyclosporine compared with 54% among 24 patients given methotrexate alone (P = .01), and no patient given methotrexate/cyclosporine had grade 4 acute GVHD. The reduction in acute GVHD had a beneficial effect on early survival. The current update with follow-up ranging from 9 to 12 years shows that the early survival advantage has persisted. Seventy-three percent of methotrexate/cyclosporine-treated patients are alive compared with 54% of methotrexate-treated patients. In all but 2 patients, chronic GVHD has resolved in response to immunosuppressive therapy.

Forty-six patients were randomized into the study from December 14, 1981 to March 14, 1985. Details on patient characteristics have been published.[1] All were conditioned for transplant by cyclophosphamide, 50 mg/kg body weight intravenously on each of 4 successive days. Thirty-six hours after the last dose of cyclophosphamide, marrow was infused intravenously. Postgrafting immunosuppression was assigned by random permutations of a set of numbers known only to the protocol registrar. Assignment was stratified by patient age (median ages 22 versus 24 years), history of preceding transfusions (19 versus 16 transfused patients), and results of the relative response index in mixed leukocyte culture. In patients given methotrexate alone, the drug was administered at 15 mg/m^2 intravenously on day 1, 10 mg/m^2 on days 3, 6, and 11, and then once weekly until day 102. In patients given methotrexate/cyclosporine, the same schedule of methotrexate was administered through day 11, when the drug was discontinued. Cyclosporine was begun on the day before grafting and was given intravenously at 1.5 mg/kg every 12 hours until patients were given oral cyclosporine at 6.25 mg/kg every 12 hours until day 50. After day 50, cyclosporine was reduced by 5% per week, and the drug was scheduled to be discontinued at 6 months. For most of the study, Food and Drug Administration regulations prohibited the use of cyclosporine in children 12 years and younger.

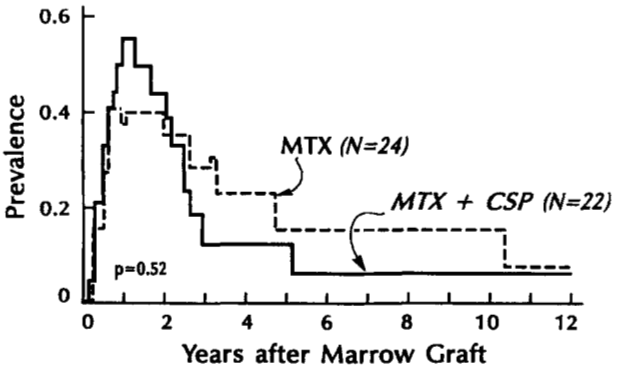

Fig 1. Prevalence of chronic GVHD among patients with aplastic anemia who were administered marrow grafts from HLA-identical siblings with either methotrexate/cyclosporine (MTX + CSP) or methotrexate alone (MTX) for GVHD prophylaxis.

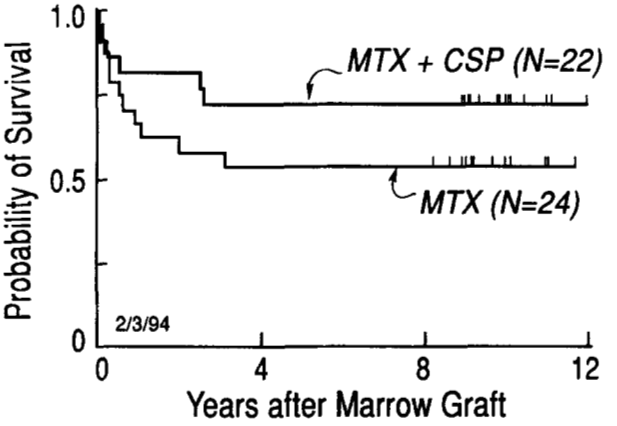

Fig 2. Kaplan-Meier product limit estimates of survival among patients with aplastic anemia who received marrow grafts from HLA-identical siblings with either methotrexate/cyclosporine (MTX + CSP) or methotrexate alone (MTX) for GVHD prophylaxis. Tick marks indicate surviving patients as of January 1994.

Two methotrexate/cyclosporine-treated patients rejected their grafts. Both were successfully retransplanted 7 months and 20 months after the first transplant, respectively, and are alive with Karnofsky scores of 100%. One methotrexate-treated patient rejected. A second transplant took place 6 months after the first; however, the patient died from complications associated with GVHD. Figure 1 shows prevalence curves describing the onset of chronic GVHD and its resolution in response to therapy.[2,3] Curves are almost identical for the two study arms (P = .52). Currently, 1 patient per study arm continues on immunosuppression. Figure 2 shows the survival curves. Although the difference did not reach statistical significance (one-sided) (P = .11), survival of methotrexate/cyclosporine-treated patients was better than that of methotrexate-treated patients. Fifteen of 16 surviving methotrexate/cyclosporine-treated patients have Karnofsky performance scores of 100%, and 1 of 90%. Nine of 13 surviving methotrexate-treated patients have scores of 100%, two of 90%, one of 80%, and one of 20%. Six methotrexate/cyclosporine-treated patients died, 1 with multiple bacterial/fungal brain and liver abscesses on day 3 after transplant, 1 with hemorrhage on day 12, 1 with interstitial pneumonia, and 3 from infectious complications associated with chronic GVHD. By comparison, 11 methotrexate-treated patients died, two from cytomegalovirus interstitial pneumonia with acute GVHD, 1 from idiopathic interstitial pneumonia without acute GVHD, and 8 from other infections, associated in 6 with acute, and in 2 with chronic GVHD.

We conclude that patients with aplastic anemia given HLA-identical marrow grafts and treated with methotrexate/cyclosporine had a significantly decreased incidence and severity of acute GVHD along with a decrease in transplant-related mortality compared with patients administered methotrexate alone. Methotrexate/cyclosporine

failed to reduce the incidence of chronic GVHD. With observation times ranging from 9 to 12 years, most patients who developed chronic GVHD have shown resolution of their disease after immunosuppressive therapy. Overall, methotrexate/cyclosporine has resulted in improved long-term survival of patients given marrow grafts for aplastic anemia compared with methotrexate alone, analogous to the previously reported improvement in long-term survival in patients transplanted for chronic myelocytic leukemia and given the drug combination.[4]

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