HEPATIC FAILURE AFTER BONE MARROW TRANSPLANTATION

To the Editor:

The article by Beelen et al. led us to report a case in which the busulfan plus cyclophosphamide preparative regimen for allogeneic bone marrow transplantation terminated in fatal hepatotoxicity.

A 31-year-old man with chronic myelogenous leukemia in first chronic phase was bone marrow transplanted from a one DR mismatched donor. Based on encouraging results obtained by Santos et al. and Tutschka et al., busulfan plus cyclophosphamide regimen was used as conditioning instead of regular cyclophosphamide plus total body irradiation. The protocol was used as described previously.2,3 Cyclosporin-A (with blood level monitorization) and methotrexate were administered for immunosuppression. The patient had an uneventful course during conditioning and infusion of the allogeneic marrow. At day +2 the patient began to experience severe fatigue and right upper abdominal discomfort accompanied by jaundice. Laboratory findings at that time were as follows: total bilirubin, 5 mg/dL; conjugated bilirubin, 2.1 mg/dL; nonconjugated bilirubin, 2.9 mg/dL; alkaline phosphatase, 52 U/L; ALT, 53 U/L; AST, 41 U/L; GGT, 114 U/L; BUN, 24 mg/dL; creatinine, 1.2 mg/dL. He was on ketoconazole prophylaxis 200 mg orally twice per day. All acute viral hepatitis markers, Epstein-Barr virus, cytomegalovirus IgG and IgM antibodies were negative. Methotrexate was discontinued. No evidence of graft-versus-host disease was observed except for high fever with negative cultures. The patient’s bilirubin levels continued to rise with normal levels of ALT and AST, and at day +9 his conjugated bilirubin was as follows: 7 mg/dL; nonconjugated bilirubin: 13.5 mg/dL; ALT, 18 U/L; AST, 26 U/L, alkaline phosphatase, 32 U/L; GGT, 33 U/L; and a steady rise in BUN and creatinine was observed. Cyclosporine was discontinued at day +7 because of the increase in blood levels due to hepatic and renal toxicity. No hepatomegaly was detected. Despite all efforts the patient died at day +10 with massive bleeding. Antemortem biopsy showed degenerative and regenerative changes and biliary pigment accumulation in hepatocytes. Portal areas had no findings related to leukemia or viral hepatitis. The findings were accepted to be consistent with reactive hepatitis.

We conclude that although very satisfying results are obtained by this preparative regimen, such fatal toxicities can be experienced.

REFERENCES


RESPONSE

As has been described in our report, the regimen originally described by Tutschka et al. was not associated with severe liver toxicity as conditioning before autologous bone marrow transplantation for acute myeloid leukemia in first remission. Meticulous revision of the published information on this issue led us to conclude that the higher dose of cyclophosphamide (200 mg/kg of body weight) described by others contributed to increased liver toxicity using a combined busulfan/cyclophosphamide regimen. Unfortunately, Dr Sardas et al. did not include any information about the exact doses of cyclophosphamide and busulfan that were administered to their patient. In addition, this case report does not describe conclusively the causative role of the conditioning regimen on the observed toxicity. Further, it remains uncertain whether the fatal bleeding complication was caused by therapy-related toxicity. Therefore, we feel unable to recognize that this case report allows valid conclusions concerning the influence of cyclophosphamide and busulfan on liver toxicity after bone marrow transplantation. It also has to be considered that the toxicity of this regimen might be substantially influenced by factors inherent to allogeneic transplantation, such as immunosuppressive drugs or liver involvement with acute graft-versus-host disease, etc.

In accordance with Dr Tutschka et al., we did not observe fatal liver toxicity in a cohort of 34 patients with leukemia after allogeneic transplantation, which further supports the assumption that the lower dose of cyclophosphamide is associated with a comparatively low rate of adverse effects on liver function. Thus, to our experience in a total of 69 patients (as of March 1990), this regimen is relatively well-tolerated in settings of autologous and allogeneic transplantation, and provides a reasonable alternative to regimens using total body irradiation.

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