To the Editor:

Veno-occlusive disease of the liver (VOD) belongs to the early complications of bone marrow transplantation (BMT) for hematologic malignancies. VOD, a thrombotic syndrome characterized by painful hepatomegaly, ascites, weight gain, and hyperbilirubinemia, is generally ascribed to the endothelial and hepatocyte damage induced by pretransplant high-dose chemoradiotherapy.

So far, no predictive parameters for the occurrence of VOD have been detected. However, Holler et al. claimed that increased serum levels of tumor necrosis factor-α (TNF-α) precede the major complications of BMT, including VOD. But, in that study, only 1 of 56 patients had VOD, whereas the others had interstitial pneumonitis, graft-versus-host disease (GVHD), etc.

There is evidence that TNF-α may be involved in the occurrence of the thrombotic complications arising after BMT. In fact, TNF-α infusion in humans strongly promotes procoagulant activity and suppresses endothelial cell surface anticoagulant activity by blocking the protein C pathway through the suppression of thrombomodulin synthesis. Furthermore, in a previous study, we clearly demonstrated the existence of a hypercoagulable state in patients undergoing BMT for hematologic malignancies.
On this basis, we evaluated the TNF-α plasma levels of the same patients of that study in order to assess the role of TNF-α as a predictive parameter of VOD occurrence.

TNF-α was analyzed before transplant, on day 0, and weekly for 1 month after transplant by an immunoradiometric assay kit (IRMA; Medgenix Diagnostics, Brussels, Belgium). The limit of detection is 5 pg/mL.

The TNF-α plasma levels were monitored in patients undergoing autologous (20 cases) and allogeneic (10 cases) BMT. Conditioning regimens were varied and mainly based on busulphan and cyclophosphamide and BAVC regimens. GVHD prophylaxis consisted of cyclosporin (CsA) and short-course methotrexate. Two patients (acute lymphoblastic leukemia and multiple myeloma; cyclophosphamide and busulphan as conditioning regimen) developed classical VOD on day +21 and on day +24, respectively. VOD was diagnosed as described by Jones et al.

As shown in Fig 1, both allogeneic (15.6 ± 4.5 pg/mL) and autologous (16.9 ± 4.9 pg/mL) patients showed mean TNF-α plasma levels significantly (P < .01) increased with respect to normal values (10.3 ± 4.4 pg/mL) at baseline time. The analysis of variance within each group showed a significant decrease of TNF-α values in the autologous group (from 16.9 ± 4.9 pg/mL before transplant to 11.4 ± 3.7 pg/mL on day +21; P < .01 - F 3.95), whereas allogeneic patients did not show any significant variation. The two patients who developed VOD had high levels at baseline time (28 and 39 pg/mL) on day 0, and weekly for 1 month after transplant by an immunoradiometric assay kit (IRMA; Medgenix Diagnostics, Brussels, Belgium). The limit of detection is 5 pg/mL.

The two patients who developed VOD showed increased pretransplant TNF-α levels and, starting from day 0, the values were much more elevated than those of the other patients. These data suggest that probably pretransplant-related events and the conditioning regimen greatly influenced the monocyte-macrophage system, leading to an increased TNF-α secretion. Although based on a small number of observations, our findings suggest that TNF-α contributes to VOD occurrence, considering the well-known procoagulant activity of this cytokine.

It has been described in experimental studies in mice that CsA prevents TNF-α release in vivo and in vitro without interfering with TNF mRNA accumulation. However, CsA, which we used in all the allogeneic BMT, did not significantly modify the plasma levels of TNF. Thus, it is likely that immunologic events related to allogeneic BMT play an important role in the TNF-α release, causing elevated levels despite the immunosuppressive therapy.

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Fig 1. TNF-α plasma levels (mean ± 1 SD) in 30 BMT patients. (●) Allogeneic BMT; (■) autologous BMT. Single TNF-α values of the two patients who developed VOD on day +21 (△) and +24 (○).

REFERENCES


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High plasma levels of tumor necrosis factor-alpha may be predictive of veno-occlusive disease in bone marrow transplantation [letter]

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