TUMOR NECROSIS FACTOR α IN HUMAN BONE MARROW RECIPIENTS

To the Editor:

In a recent article, Holler et al[1] conclude that tumor necrosis factor α (TNF-α) is a predictive marker of major transplant-related complications (TRC). In the same issue of *Blood,* Hervé et al[2] investigated the role of interleukin-2 (IL-2) in the pathogenesis and treatment of acute graft-versus-host disease (AGVHD). Recently we have started to monitor allogeneic bone marrow transplant patients with serum soluble IL-2 receptor (Cell free; T cell sciences, Cambridge, MA) and TNF-α (Biokine; T cell sciences) levels. Seven patients were analyzed, three of which experienced major TRC. Serum samples immediately after separation were kept at −80°C until assay time. Pretransplant and highest early and late posttransplant values are shown in Table 1. Despite a normal pretransplant value, the pathologic increase in patient 3 was in accordance with the results of Holler et al. However, the other complicated cases showed neither such an increase nor any predictive sign of TRC. As these authors have already discussed, the issue of serum cryopreservation does not explain the normal levels of TNF-α in our patients. Although none of these patients exhibited AGVHD, sIL-2 was high in six of the patients. Except for the aplastic anemia patient, none of the patients had cytomegalovirus (CMV) antigenemia, detected by Immunperoxidase (Clonab CMV, biotest). As all donor and recipients were CMV seropositive, they received prophylactic or therapeutic (patient no. 7) hyperimmune CMV globulin (Cytotech; Biotest, Frankfurt, Germany). Finding the mechanism that triggers IL-2R secretion may explain inhibition of hematopoiesis in these complicated cases.[3] However, the transient and lesser increase in the uncomplicated transplants needs further investigation.

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Table 1. TNF-α and sIL-2R Levels in Our Patients

Diagnosis	Complication	TNF-α (pg/mL)		Soluble IL-2R (IU/mL)		
				Early		Late
		Pre	Post	Pre	Post	Post
ALL	Primary graft failure	15	50	2,500	2,400	—
ALL	Primary graft failure + CMV infection	35	20	790	1,560	—
Hodgkin + myelofibrosis	Endothelial leakage syndrome	20	100	2,500	2,500	—
ANLL-M2	None	30	30	890	1,620	500
ANLL-M3	None	25	50	450	1,130	410
ALL	None	40	45	230	260	190
Aplastic anemia	None	45	45	2,500	2,500	2,500

Abbreviations: Pre, pretransplant; Post, posttransplant; ALL, acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia.

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RESPONSE

Sardas et al report their experience with monitoring serum levels of tumor necrosis factor α (TNF-α) and soluble interleukin 2-receptors (IL-2R) in human bone marrow transplantation (BMT). In their study, three patients developed transplant-related complications (TRC): one patient with endothelial leakage syndrome showed an increase of TNF-α levels, confirming observations reported in our

paper; two patients developed primary graft failure, one associated with cytomegalovirus (CMV)-infection. In primary graft failure, bacterial or fungal infectious are the most frequent TRC. Our analysis showed lower TNF-α levels in patients with infections without typical further endothelial TRC or acute graft-versus-host disease (AGVHD), and only CMV infections associated with interstitial pneumonitis were preceded by an increase of TNF-α levels. Thus, in our view, the data reported by Sardas et al are not contradictory to results published in our study.

In addition, we were able to confirm our analysis of TNF-α release in human BMT by prospective monitoring of fresh samples in further 64 patients.[1] Loss of TNF-α activity by cryopreservation was particularly observed for fresh samples containing less than 300 pg/mL TNF-α as seen in patients without AGVHD and TRC. However, in patients with severe TRC maximal TNF-α levels were comparable in both studies.

A further concern is raised with regard to the assay system used for cytokine monitoring. Some commercial assays (including the one used by Sardas et al) use sample buffers containing serum proteins that proved to interfere with detection of TNF-α in our laboratory. In addition, acute-phase proteins and soluble inhibitors may interfere depending on the type of assay and monoclonal antibodies used. In our view, standardization of TNF-α assays is urgently needed to allow comparison of clinical studies performed with different assays. We have compared serum levels obtained by our TNF-α–enzyme-linked immunosorbent assay (ELISA) with cytotoxicity using L929 cells, and found a good correlation for ELISA levels greater than 100 pg/mL with bioactivity.[1]

With regard to IL-2R levels, several groups have reported elevated levels after BMT during infections as well as in the course of AGVHD.[2,3] Thus, specificity of IL-2R levels seems to be inferior to TNF-α levels, as also observed by Sardas et al.

Because of the complex regulation of TNF-α and the unknown pathophysiologic role of humoral antagonists, individual serum levels cannot be used for precise prediction of TRC in a single patient. However, they proved to be useful to identify patients with enhanced risk of TRC in our unit, which should allow development of risk-adapted therapeutic and prophylactic strategies in the future.

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