Haematologica 1998; 83:1082-1087 original paper

IL-6 and IL-8 levels in plasma during hematopoietic progenitor transplantation

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ABSTRACT

Background and Objective. **The relationship between cytokine concentrations and transplant-related complications has been studied in bone marrow transplant patients. The changes in TNF-α, IL-1 and IL-6 concentrations after transplantation are well documented in the literature but this is not the case for IL-8. The purpose of the present study was to investigate prospectively the plasma concentration of these cytokines and their relationship to transplant-related complications.**

Design and Methods. **Pro-inflammatory cytokine (TNF-α, IL-1, IL-6 and IL-8) levels in plasma were determined in a group of 53 patients undergoing hematopoietic progenitor transplantation. Plasma samples were collected weekly from day –7 to day +35 and stored at –70 ºC until assayed by ELISA. The major transplant-related toxicities registered were: veno-occlusive disease (VOD), acute graft-versus-host disease (GVHD), infectious episodes, renal failure and mucositis.**

Results. **In spite of the great variability of plasma cytokine profiles between the different patients, we came to various conclusions. Patients' TNF-α and IL-1 concentrations correlated well over time. IL-6 and IL-8 profiles were similar and correlated well with febrile episodes. In some cases, an increase in IL-6 preceded hematologic recovery. In our study, increased levels of TNF-α, IL-6 and especially IL-8 correlated with hepatic or renal dysfunction as evaluated by increased bilirubin and creatinine in plasma, while pulmonary complications correlated only with increased IL-6 levels. Allogeneic transplant patients had a tendency to have higher TNF-α concentrations than autologous transplant patients, probably because an allogeneic transplant is associated with more transplant-related toxicity. Basal disease usually had no effect on cytokine profiles.**

Interpretation and Conclusions. **IL-6 and IL-8 were the only cytokines studied whose increase correlated with febrile episodes. High IL-8 values may be a useful predictor of renal dysfunction and pulmonary disease and seems to trigger off high IL-6 levels. Plasma TNF-α and IL-1 concentrations during the post-transplant period have not been shown to be predictive of the development of transplant-related complications, and none of the profiles was recognized to be specific for a particular complication in this study.**

Key words: cytokines, IL-1, IL-6, IL-8, hematopoietic progenitor transplant

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Cytokines are low molecular weight glycoproteins involved in inflammatory and immune responses. Some cytokines have a stimulatory effect on hematopoiesis and behave as growth factors.[1] They are predominantly produced by lymphocytes and mononuclear phagocytes and stimulate or suppress different kinds of inflammatory responses interacting within a complicated network.

The dysregulation of cytokine production seems to be involved in the rejection or tolerance of grafts,[2] and in the initiation and perpetuation of tissue damage in bone marrow and solid organ transplants.[3]

Tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8) are well known pro-inflammatory cytokines involved in local and systemic inflammatory reactions. This fact has been found to be especially important in endotoxemia.[4,5] TNF-α, IL-1, IL-6 and IL-8 are also involved in many adverse conditions proceeding from a hematopoietic progenitor transplant such as infections, mucositis, hepatic veno-occlusive disease (VOD) and graft-versus-host disease (GvHD). TNF-α, IL-1 and IL-6 levels after transplantation have been widely determined, but IL-8 levels less so. A detailed comparison of cytokine plasma levels showed a very high variability that hindered further analysis.[6-10]

We studied the relationship between plasma concentrations of pro-inflammatory cytokines (TNF-α, IL-1, IL-6 and IL-8) and transplant-related complications in a group of 53 patients undergoing hematopoietic progenitor transplant, in order to clarify the behavior of these cytokines after a bone marrow or peripheral blood stem cell transplant.

Materials and Methods

Patient selection

We studied 53 patients with a hematologic malignancy undergoing a bone marrow (BM) or peripheral blood stem cell (PBSC) transplant between September 1993 and March 1995 in our center.

Blood sample collection

Blood samples were collected in tubes containing EDTA and sodium citrate, on days -7, -1, +1, +7, +14, +21, +28 and +35 and stopped when hematologic recovery was established. Samples were placed on ice, centrifuged within 2 hours of blood collection, and then transferred to microfuge tubes and frozen at –70°C until assayed.

Definition of major transplant-related complications

The diagnosis of hepatic VOD required the presence of hyperbilirubinemia (>3.0 mg/dL), weight gain (>2.5% of initial weight) and right upper quadrant pain with or without the presence of hepatomegaly.[11] GvHD was evaluated following the updated acute GvHD grading system proposed by Przepiorka *et al.*[12] Severity of mucositis was scored in accordance with previously published criteria.[13]

Table 1. Description of patients' characteristics, conditioning therapy and graft-versus-host disease (GvHD) prophylactic regimen.

Characteristics	*N (%)*
Sex, M/F	39/14
Hematopoietic transplant:	
allogeneic BM	27 (51%)
autologous BM	16 (30%)
autologous (PBSC)	10 (19%)
Basal disease:	
ALL	15 (28%)
CML	14 (26%)
AML	8 (15%)
NHL	6 (11%)
HD	5 (9%)
Other	5 (9%)
Conditioning therapy:	
CY/TBI	43 (80%)
BU/MELPH/THIOT	4 (8%)
CBV	2 (4%)
OTHER	4 (8%)
GVHD prophylaxis*	
CsA + MTX + PDN + T cell depletion	11 (41%)
CsA + MTX + PDN	9 (33%)
CsA + MTX	5 (19%)
CSA + MTX + T cell depletion	2 (7%)

**Only for allogeneic transplants (27 patients).*

Determination of TNF-α, IL-1, IL-6 and IL-8 levels

TNF-α, IL-1, IL-6 and IL-8 plasma levels were determined by a double antibody sandwich ELISA (Immunotech International, Montpellier, France), following the manufacturer's instructions. Briefly, calibration standards were prepared by dilution of a stock solution of cytokine and a monoclonal anti-cytokine capture antibody was attached to the surface of the wells of a microtiter plate. Standard or serum samples were added to the wells and incubated with an anti-cytokine monoclonal antibody conjugated to alkaline phosphatase. Finally, after the incubation and washing steps, the substrate was added to each well. The reaction was stopped with NaOH and the absorbance of the wells was measured at 450 nm. Cytokine concentrations in the test samples were determined by comparison with the standard curve obtained from the controls.

Statistical analysis

The correlations between numerical variables were assessed using the Spearman rank test. The Wilcoxon signed rank test was also used when variables did not follow a normal distribution. Differences were considered statistically significant when $p<0.05$.

Results

Patients' description

Patients' characteristics, conditioning therapy, and graft-versus-host disease prophylactic regimens are described in Table 1.

The average age of the patients studied was 32.4 years (range: 15-59). Of the 53 patients, 27 (51%) had allogeneic transplants and the other 26 (49%) had an autologous transplant of peripheral blood or bone marrow stem cells. Most of the patients suffered from acute (23 patients) or chronic (14 patients) leukemia. The most frequently used conditioning therapy consisted of cyclophosphamide and total body irradiation (TBI).

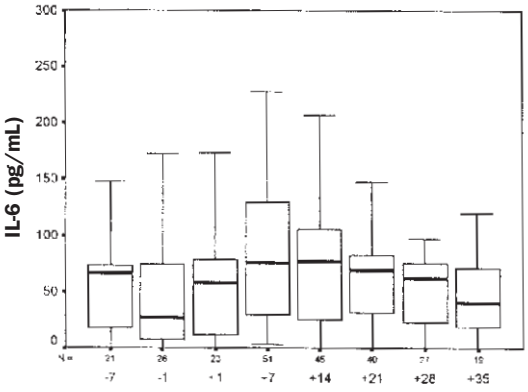
Plasma cytokine concentrations

TNF-α, IL-1, IL-6 and IL-8 concentrations were determined in 270 plasma samples from 53 patients undergoing hematopoietic transplantation and are shown in Figure 1.

The plasma profiles of the four cytokines showed a great variability between the different patients.

Plasma levels of TNF-α and IL-1 on day -7 showed a strong positive correlation with the subsequent concentrations of TNF and IL-1 respectively. Patients with high TNF-α and IL-1 levels at the beginning of the transplantation retained these high levels throughout the procedure. This correlation was not observed as clearly for IL-6 and IL-8 (data not shown).

The correlation coefficients between IL-6 and IL-8 reached statistical significance on the same day of measurement for days +1 ($r=0.46$, $p<0.05$), +7 ($r=0.64$, $p<0.005$), +14 ($r=0.62$, $p<0.005$), +21



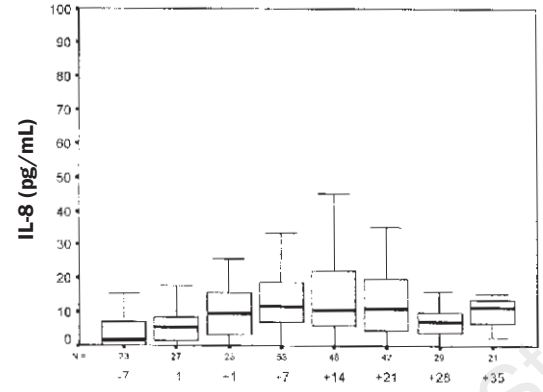


Figure 1.

(r=0.49, p<0.005) and +28 (r=0.36, p<0.1). The profile of both cytokines was very similar in each patient.

Relationship between plasma cytokine levels and transplant-related complications

High plasma TNF-α concentrations seem to predict the severity of the mucositis after transplantation from very early stages, i.e. days –1 (r=0.46, p<0.026), +14 (r=0.29, p<0.041) and +21 (r=0.39, p<0.033). The same positive correlation was also observed between mucositis and IL-6 plasma levels on days –1 (r=0.39, p<0.07), +1 (r=0.42, p<0.043) and +14 (r=0.34, p<0.028).

No clear correlation was detected between mucositis and IL-1 or IL-8 plasma concentrations. Figure 2 shows the evolution of the four cytokine levels throughout the study period in two patients, one who suffered from fever, and one who did not.

IL-6 and IL-8 profiles proved to be good indicators of febrile episodes. In all the patients with a febrile episode the mean plasma cytokine levels determined on the first day studied before and after the first febrile episode showed a significant increase in IL-6 and IL-8 concentrations (Table 2). This was not observed for TNF-α or IL-1. Although not statistically significant, IL-6 levels tended to be higher in the patients who died of infection than in those who died of acute graft-versus-host disease (data not shown).

Table 2. Mean plasma cytokine concentrations determined on the first day studied before (BF) and after (AF) the first febrile episode (SD=standard deviation).

	Mean	*SD*	*Minimum*	*Maximum*	
TNF (BF)	51.86	32.27	13.2	145.6	
TNF (AF)	48.94	30.78	14.4	165.4	t=0.15, p=0.878
IL-1 (BF)	17.04	41.40	0	203.9	
IL-1 (AF)	13.35	23.40	0	121	t=0.06, p=0.955
IL-6 (BF)	66.91	71.01	0	370	
IL-6 (AF)	140.54	133	11.8	520	t=3.34, p=0.002
IL-8 (BF)	11.18	12.3	0	49.5	
IL-8 (AF)	49.36	86.98	0	520	t=3.13, p=0.004

In 4 out of 6 patients with no febrile episodes during the transplantation period, IL-6 and IL-8 concentration peaks preceded the granulocyte recovery (Figure 2).

There was a positive correlation between IL-6 and IL-8 levels, and bilirubin values on the same days. IL-6 and bilirubin positively correlated on days +7 (r=0.26, p<0.1), +21 (r=0.41, p<0.1) and +28 (r=0.38, p<0.05). A stronger correlation was established between IL-8 and bilirubin levels on days +7 (r=0.47, p<0.05), +14 (r=0.31, p<0.05), +21 (r=0.37, p< 0.05) and +28 (r=0.072, p<0.005). Although the correlation coefficients are not very high, elevated levels of IL-6 and IL-8 preceding the transplant seem to predict renal dysfunction (Table 3). The only cytokine that showed a relationship with the onset of pulmonary complications (pneumonia or pulmonary hemorrhage) was IL-6, as the plasma levels of this cytokine were higher on days –7 (70.9±3.8 pg/mL vs. 50.6±43.6 pg/mL, p<0.069), –1 (84.6±22.0 pg/mL vs. 37.5±43.4 pg/mL, p<0.048), +14 (276.9±362.8 pg/mL vs. 88.5±100.2 pg/mL, p<0.260) and +21 (213.3±226.2 pg/mL vs. 85.5±114.5 pg/mL, p<0.092) of the transplantation in patients with these complications. No relationship between the different cytokines and the onset or severity of acute GvHD was observed in our data (not shown).

Relationship between plasma cytokine levels and basal disease or kind of transplant

Basal disease did not show an important effect on cytokine profiles.

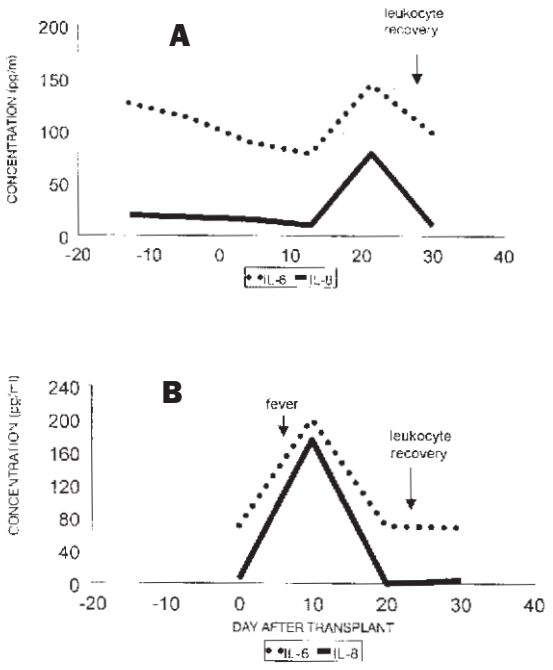


Figure 2.
A: evolution of IL-6 and IL-8 levels in plasma in a patient who did not develop fever.
B: evolution of IL-6 and IL-8 levels in plasma in a patient who did develop fever.

Plasma TNF-α concentrations were higher in patients undergoing an allogeneic transplant than in those receiving an autologous hematopoietic progenitor transplant. This was particularly noticeable on days +1 (59.6±40.3 pg/mL vs. 39.2±18.0 pg/mL, p<0.114), +14 (58.0±25.8 pg/mL vs. 46.0±19.5 pg/mL, p<0.080) and +21 (60.3±24.3 pg/mL vs. 46.7±21.5 pg/mL, p<0.068). No differences in the plasma levels of IL-1, IL-6 or IL-8 according to by the different basal diseases or the type of transplant were detected.

Discussion

Plasma TNF-α, IL-1, IL-6 and IL-8 levels were studied in a group of 53 patients undergoing a bone marrow or peripheral blood stem cell transplant.

A strong correlation between IL-6 and IL-8 levels in plasma was observed in this study throughout the study period. IL-6 and IL-8 profiles correlated well with febrile episodes in this study, with higher levels of IL-6 in the plasma of patients who died of infection than in those who died of acute GvHD. Cytokines were also related to the hematologic recovery.

The levels of TNF-α, IL-1 and IL-6 in plasma or serum after a hematopoietic transplant have been reported by many groups,[6,8,14-18] but little attention has been paid to IL-8 detection.[9,10]

According to some authors, patients experiencing major organ toxicity after a transplant such as infection, endothelial leakage syndrome, veno-occlusive disease, GvHD or pneumonia, are supposed to have higher TNF-α levels than those patients without major organ toxicities.[7,14] Other authors, including those of the present study, have not observed this relationship.[8,15]

TNF-α and IL-1 are known inducers of IL-6 and IL-8 production, while IL-6 is a strong inhibitor of TNF-α and IL-1, and due to this negative feed-back, IL-6 is a factor which limits hyperactivation of the proinflammatory cytokine cascade.[19] IL-6 has no stimulatory effect on IL-8, therefore, probably the same agents are stimulating IL-6 and IL-8 production in parallel. However, we detected a positive correlation between plasma concentrations of TNF-α and IL-6 and severity of mucositis, a correlation which was not observed for IL-8.

Intravenous administration of endotoxin to healthy human volunteers causes an increase in TNF-α, IL-6 and IL-8 plasma levels.[4,20] In non-hematologic patients admitted to an intensive care unit, IL-6 and IL-8 plasma levels were higher in septic patients.[21] Many studies have pointed out a strong correlation between IL-6 and/or IL-8 concentrations and the onset of infectious complications in patients with hematologic malignancies and chemotherapy-induced leukocytopenia.[5,8,22-24] The same finding has been confirmed in patients undergoing a bone marrow or peripheral blood stem cell transplant presenting with infectious episodes.[9,15,17,18] Some authors have detected very high IL-6 levels in patients with Gram-negative bacteremia.[5,24,25] We were unable to detect such differences (data not shown).

In this study, pulmonary disease caused increased values of IL-6 in plasma, a finding which has not been previously reported in the literature.

IL-6 is an important component in the regulation of normal hematopoietic activity. It has positive

Table 3. Correlation coefficients between interleukin-6 (IL-6) and interleukin-8 (IL-8) plasma concentrations and renal dysfunction evaluated by increased creatinine levels in plasma.

IL-6 (+14) and creatinine (+7)	r = 0.28*
IL-6 (+14) and creatinine (+21)	r = 0.36°
IL-6 (+21) and creatinine (+28)	r = 0.33*
IL-6 (+28) and creatinine (+28)	r = 0.50°
IL-8 (-1) and creatinine (+1)	r = 0.89°
IL-8 (-1) and creatinine (+21)	r = 0.45°
IL-8 (-1) and creatinine (+28)	r = 0.53°
IL-8 (-1) and creatinine (+35)	r = 0.66°
IL-8 (+21) and creatinine (+28)	r = 0.48°
IL-8 (+21) and creatinine (+35)	r = 0.42*

**0.05 < p < 0.1; °0.005 < p < 0.05; #p< 0.005.*

effects on thrombopoiesis[19] and supports the granulocytic differentiation of hematopoietic progenitor cells.[26] In some patients who did not have any febrile episodes during the transplantation procedure, we observed IL-6 and IL-8 plasma peaks preceding the hematologic recovery (as evaluated by an increase in neutrophil count) as Steffen *et al*.[18] also reported.

We observed a positive correlation between IL-6 or IL-8 levels and bilirubin or creatinine concentrations. Similar findings concerning IL-6 and hyperbilirubinemia have been reported[18] in the literature. Increased plasma IL-8 levels on day –1 seemed to predict renal impairment after transplantation in our patients.

Remberger *et al.*[10] reported high levels of IL-8 in patients developing VOD. In this study only 3 patients were diagnosed as having VOD and this relationship could not be confirmed. High IL-8 levels were, however, found in plasma of patients with high bilirubin values, which indicate early liver damage.

TNF-α, IL-1 and IL-6 probably play important roles in the initiation and progress of GvHD as in other immunologic reactions, but it is also probable that a more complex relationship exists between cytokine production and other biological events in GvHD which confounds the assignment of exact roles to the different cytokines. No direct association was seen between plasma levels of TNF-α, IL-1, IL-6 and IL-8 and acute GvHD in the present study or in others.[8,17] It has been suggested that the analysis of cytoplasmic TNF-α and IL-1 levels in peripheral blood mononuclear cells could be a more reliable marker of GvHD than serum or plasma cytokine concentrations.[15]

Imamura *et al.*[16] determined the serum levels of TNF-α, IL-1α, IL-6 and IFN-γ in patients receiving a bone marrow transplant and observed a rise of IL-6, IFN-γ and IL-1α in patients developing GvHD. They reported that patients receiving an allogeneic transplant had higher TNF-α concentrations than patients receiving an autologous transplant, probably owing to a higher incidence of transplant-related complications with the allogeneic procedure. We found the same tendency.

We did not find a different pattern of cytokine secretion depending on the *ex vivo* manipulation of the hematopoietic progenitors, although this study only involved a small number of patients. This result is in agreement with the similar serum levels of TNF-α and IL-6 found by Schwaighofer *et al*.[27] in T-cell depleted and non-T-cell depleted bone marrow transplants.

The variability of plasma cytokine levels between patients in the literature may also be related to the different immunologic assays used. ELISA is a method that can detect inactive forms of the cytokine and does not detect *in vivo* antagonists of the different cytokines.[28] Moreover, the use of serum or plasma and the sample processing protocol may influence the results of immunoassays.

In conclusion, IL-6 and IL-8 were the only cytokines studied whose increase correlated with infectious episodes. High IL-8 levels may be a useful predictor of renal dysfunction and pulmonary disease seems to trigger off high IL-6 levels in plasma. Plasma TNF-α and IL-1 concentrations during the post-transplant period were not shown to be predictive of the development of transplant-related complications, and none of the profiles was recognized to be specific for a particular complication.

Contributions and Acknowledgments

CF was responsible for the conception of the study, its design, ethical approval, recruitment of and day-to-day contact with participants, interpretation of the study and writing the paper. SS carried out analysis and interpretation of the data and collaborated with the writing of the paper. AG collaborated in the study design, was responsible for funding and direct supervision and was the principal clinician involved. FR and JG carried out the ELISA procedures. DG, JB, DM, EdlB, IA and JP were involved in clinical assessment of the patients. We would like to thank all the staff nurses and residents of the Department of Hematology at the Hospital "Duran i Reynals" for their collaboration in this study.

Funding

Fundación Internacional José Carreras para la Lucha contra la Leucemia, FIJC/AG97.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received May 19, 1998; accepted September 10, 1998.

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