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EARLY HEMOSTATIC ALTERATIONS FOLLOWING BONE MARROW TRANSPLANTATION: A PROSPECTIVE STUDY

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ABSTRACT

Background. **The occurrence of coagulation system alterations after bone marrow transplantation (BMT), and their possible role in the pathogenesis of thrombotic complications such as the veno-occlusive disease of the liver (VOD), is still matter of debate. The aim of this study was to prospectively evaluate the alterations in hemostatic balance ensuing in the early period after BMT (up to day +21), and their relationships (if any) with VOD.**

Patients and Results. **Twenty-nine patients (15 autologous and 14 allogeneic BMT) entered the study. No patient suffered from thrombotic and/or major hemorragic events. Since there was no difference between the two groups of patients as regards modifications of coagulation parameters, they were considered as a whole group for the purposes of the study. We observed a progressive increase from basal levels of fibrinogen, factor VIII activity (fVIII:C) and von Willebrand factor antigen (vWf), while factor VIII antigen (fVIIAg), protein C, and plasminogen significantly decreased. The modifications of the tests were maximal on day +14, with a trend towards normal levels one week later. There was no modification of PT, PTT, prothrombin fragment 1+2 (F 1+2), f XIIC, tPA, PAI-1, D dimer and protein S levels; also serum levels of tumor necrosis factor-α were unmodified.**

Conclusions. **These results suggest that some alterations of the hemostatic system, likely a consequence of an endothelial damage, can be detected early after BMT, but their clinical significance remains uncertain, due to a lack of correlation between the hemostatic test alterations and the occurrence of thrombotic complications.**

Key words: bone marrow transplantation, veno-occlusive disorder, thrombosis, hemostasis, von Willebrand factor

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The occurrence of thrombotic complications after bone marrow transplantation (BMT), mainly represented by the hepatic veno-occlusive disease (VOD), has extensively been documented, although the incidence varies from 0 to more than 50% in different series.[1-6] Although the hystopathology characteristics[7] and clinical manifestations[3,5,8,9] of VOD have thoroughly been described, the pathogenesis is still poorly understood. The activation of coagulation system, likely consequent to an endothelial damage, has been proposed as the primary mechanism.[1,7] However, there is a great variability in different studies as regards the modifications of coagulation parameters in these patients,[10-17] and in most studies only selected coagulation tests were evaluated. Therefore, a more exhaustive analysis of coagulation parameters might be of help in identifying any test with some inherent predictive value of thrombotic complications after BMT.

To this end, we carried out a prospective

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study in 29 patients undergoing either autologous (ABMT; 15 patients) or allogeneic BMT (14 patients) to evaluate, by a multiparameter laboratory analysis approach, the occurrence of alterations in hemostatic balance in the first three weeks after BMT; this time interval was chosen as previous studies indicated the majority of the registered cases of VOD occurred within this early period after BMT.[1,4,5] In addition, also plasma levels of tumor necrosis-factor-α, which has been implicated in the pathogenesis of major complications after BMT, were evaluated. The results presented herein indicate that some imbalance of the hemostatic system occurs frequently after BMT, but it is not invariably associated with thrombotic events, since in no patient did they occur. Therefore, unknown additional factor(s) and/or individual characteristics are required to transform the mild hemostatic imbalance of an uncomplicated BMT in life-threating thrombotic complications, such as VOD.

Patients and Methods

Patients' characteristics and conditioning regimens employed are reported in Table 1. There were 15 ABMT and 14 allogeneic BMT patients enrolled in the study after an informed consent was obtained; these were all consecutive patients transplanted in our Unit within a one-year period who had not received hematopoietic growth factors (GM-CSF, G-CSF, or erythropoietin) following transplantation.

The adopted conditioning regimens were the followings: *BUCY*, busulphan 4 mg/Kg/day orally for 4 days + cyclophosphamide 50 mg/kg/day i.v. for 4 days; *BEAM*, BCNU 300 mg/m^2 i.v. on day –6, Ara-C 200 mg/m^2 i.v. and etoposide 200 mg/m^2 i.v. on days –5 to –2, melphalan 140 mg/m^2 i.v. on day –1; *CVB III*, BCNU 150 mg/m^2/day i.v. for 4 days, etoposide 400 mg/m^2 i.v. for 4 days, cyclophosphamide 1.5 g/m^2 i.v. for 4 days. TBI was performed by delivering eleven 120 cGy fractions in 4 days, with a 300 cGy anterior and posterior electron boost; total dose was 1320 cGy, with a dose rate of 18-19 cGy/min. In the *TBI-VP-CY* regimen, TBI was followed by etoposide, 12.5 mg/kg/i.v. twice a day for two days, and cyclophosphamide, 60 mg/kg/i.v. for two days. In the *BU-VP-CY* regimen, busulphan, 4 mg/kg/day orally on days –9 to –6, was followed by etoposide, 12.5 mg/kg i.v. twice a day on days –5 and –4, and cyclophosphamide, 60 mg/kg/day i.v. on days –3 and –2. In the *TBI-CY* regimen, TBI was followed by cyclophosphamide, 60 mg/kg/day on days –3 and –2. As a prophylaxis against graft-versus-host-disease (GVHD) in allogeneic BMT, cyclosporin-A (2 mg/kg) was given starting on day –1, while methotrexate was given on day +1 (15 mg/m^2) and on day +3, +6, +11 (10 mg/m^2).

The criteria adopted for the diagnosis of VOD

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Table 1. Patients characteristics.

	Age	*N.*	*Disease*	*Disease status*	*Conditioning regimen*
Allo-BMT	14 (M= 9) (F= 5)	34 14-51	7 AML 5 CML 2 ALL 1 RD	7 CR1 4 CR2 2 CR3 2 TBICY	9 BUCY 1 BUVPCY 2 TBIVPCY
ABMT	15 (M= 7) (F= 8)	31 1 CML 17-52	8 AML 3 CR2 3 HDG 3 NHL	6 CR1 6 BUCY I 2 CR3 2 RD 1 RL2 1 RL3	4 BEAM 3 CVBIII 1 BUVPCY 1 TBIVPCY

Age, mean and range; Allo-BMT, allogeneic bone marrow transplantation; ABMT, autologous BMT; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; ALL, acute lymphoid leukemia; HDG, Hodgkin's disease; NHL, non-Hodgkin lymphoma; CR, complete remission; RD, resistant disease; RL, relapsed disease. For details about conditioning regimens, see Text.

were those of Seattle's team,[3] that is the occurrence of at least two of the following symptoms within the first month after BMT: a) jaundice (bilirubin >27 mmol/L), b) development of hepatomegaly and right upper quadrant pain, c) ascites and/or unexplained weight gain (>5% from baseline).

For the evaluation of hemostatic parameters, blood was drawn by careful peripheral blood vein puncture using a two syringe technique, at the following times: basal, 10 days before transplantation; day 0, on the day of transplantation, just before starting graft infusion; day 7, day 14, day 21, on day +7, +14, and +21, respectively, following transplantation. Platelet poor plasma, prepared at 4°C, was stored in aliquots at –80°C before assay.

Laboratory coagulation tests: prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen determination were performed by standard laboratory methods.[18] Plasma factor VIII activity was measured by one-stage assay;[19] von Willebrand factor antigen (vWFAg) was measured using an ELISA method.[20] The dosage of factor VII antigen was accomplished by immunochemical analysis, according to Triplett et al.[21] tPA and protein S levels were quantified according to Ronby et al.[22] and Mannucci et al.[23] respectively, while TNF-alpha was assayed by commercially available kit (Technogenetics, Mi, I). Protein C, plasminogen, and PAI-1 were quantified by chromogenic methods, according to Bertina et al.,[24] Soria et al.,[25] and Chemielewska et al.,[26] respectively. D-dimer and F 1+2 levels were quantified with an Elisa method (Asserachrome, Biochemia, Mannheim).

Statistical analysis. Standard statistical techniques were used according to the CSS (Statsoft, Tulsa) program: Friedman ANOVA test was used for multiple comparisons among groups, Wilcoxon rank sum test and Mann-Whitney U test for post-hoc analysis of paired and unpaired populations, respectively. Overall differences over time (from T basal to day 21) were estimated with a test for trend.[27] A p value of <0.05 was considered to represent a significant difference. Results are expressed as mean + standard deviation (SD) throughout the text.

Results

A total of 29 patients undergoing bone marrow transplantation for hematological malignancies were prospectively studied; 14 of these were subjected to an allogeneic BMT, and 15 to ABMT. As shown in Table 1, these two groups of patients were comparable in terms of patient number, sex distribution, and age. In the BMT group, 10/14 patients were conditioned with busulphan- and the remaining 4 with TBI-including regimens, while in the ABMT group 7/15 patients received busulphan- and only 1 TBI-including regimens; 9/14 BMT and 4/15 ABMT patients were positive for HBV hepatitis, while 1 patient in each group was positive for both HBV and HCV hepatitis. Only patients not receiving hematopoietic growth factors were included in the study in order to avoid unknown interferences due to the secundary release of cytokines, including tumor necrosis factor-α, from cells stimulated with GM-CSF or G-CSF. None of the patients under study presented with symptoms and signs suggestive of VOD, nor did they suffer from major hemorragic or thrombotic events during the observation period (from day –10 up to day +28).

In the initial statistical analysis of coagulation parameter modifications, the two patient groups were managed as separate entities; thereafter, they were compared one to each other for any individual coagulation parameter and for any time point of study. Since there was no statistically significant difference between ABMT and allogeneic BMT patients, they were considered as a whole group of patients for the purposes of this study.

In Figures 1 and 2, the modifications of some coagulation parameters during the study period are reported. While pre-conditioning (basal) values were not significantly different from normal control values, there was a progressive increase of factor VIIIC and von Willebrand factor levels (Figure 1), peaking on day +14; on the other hand, a decrease of factor VIIAg (Figure 1), protein C, and plasminogen values (Figure 2) was observed during the conditioning regimen and the early post-transplant phase, peaking at day +7 after bone marrow transplantation. On day +21, factor VIIIC and von

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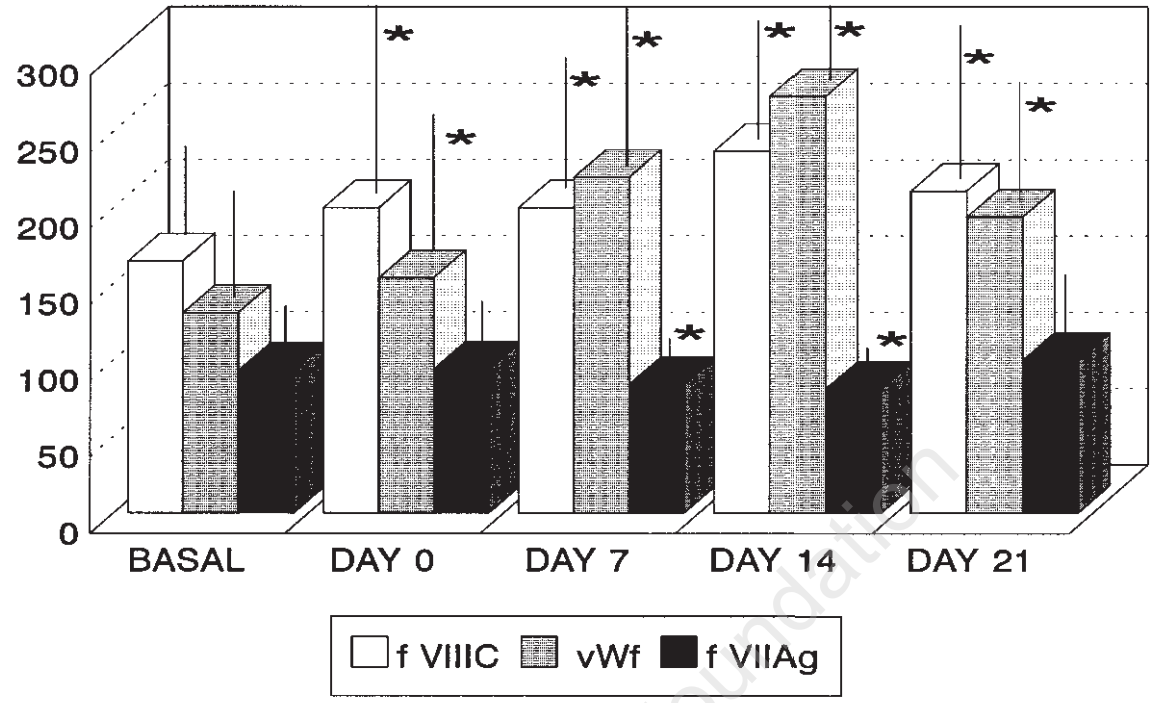

Figure 1. The modifications of f VIIIC, vWf and f VIIAg during the study. * denotes values significantly different from basal ones at p <0.05.

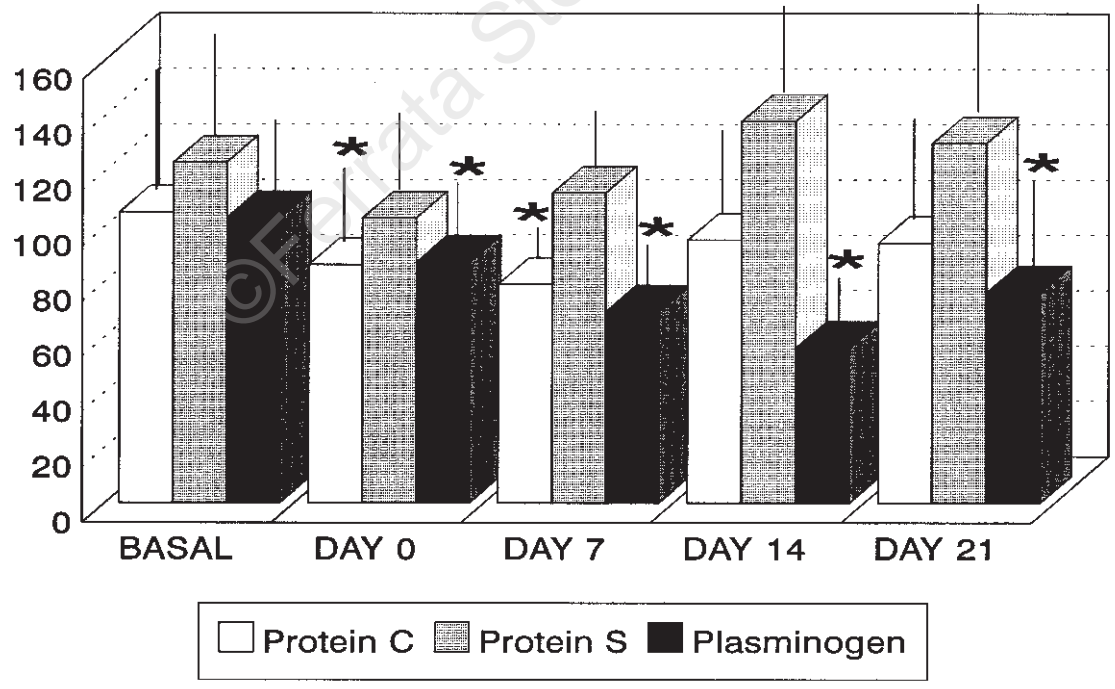

Figure 2. The modifications of protein C and S and of plasminogen levels during the study. * denotes values significantly different from basal ones at p <0.05.

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Willebrand factor still remained significantly higher than pre-treatment levels, while there was a normalization of factor VIIAg and of protein C; however, plasminogen remained significantly lower than basal levels on day +21. On the other hand, protein S did not change appreciably during the study period. Fibrinogen levels behaved essentially as factor VIIIC and von Willebrand factor, reaching a peak of 525 +144 mg/dL on day +7, and normalizing on day +21 (data not shown in detail). Finally, there was no significant modification of the other coagulation tests evaluated in this study, which are reported in Table 2.

Serum levels of tumor necrosis factor-alpha were assayed concurrently with coagulation tests; basal levels of TNF-α were comprised within the normal range (3-20 pg/mL), and did not modified significantly thereafter (data not shown in detail).

Table 2. List of coagulation parameters analyzed and resulted not significantly different from normal values at any time point of the study (values not reported in detail).

PTT (sec.)	partial thromboplastin time
PT (% activity)	prothrombin time
FP 1+2 (nM/L)	prothombin fragment 1+2
XIIC (U%)	factor XII activity
TPA (ng/mL)	tissutal plasminogen activator
PAI-1 (U/mL)	plasminogen activator inhibitor 1
D dimer (ng/mL)	D-dimer
TNF-α (pg/mL)	tumor necrosis factor-α

Discussion

Among thrombotic complications occurring after BMT, hepatic VOD, a syndrome due to fibrous obliteration of the lumina of small intrahepatic veins causing sinusoidal obstruction and intrahepatic portal hypertension, is by far the most frequent, usually developing within the first 2 to 4 weeks after transplantation. Other more infrequent thrombotic complications of BMT include a pulmonary endothelial leakage syndrome, thrombotic thrombocytopenic purpura mainly associated with cyclosporin-A therapy, and episodes of venous thromboembolism. The diagnosis of VOD still relies on clinical criteria, according to either Seattle's[3] or Baltimore's[5] group criteria, whose specificity is quite good although the sensitivity is unfortunately low; however, transjugular liver biopsy, and the measurement of the hepatic venous pressure gradient, may help to establish the diagnosis in less severe cases and in the early course.[9]

Although the pathogenetic mechanisms of VOD are not known, the role of coagulation system alterations has been advocated in the light of the immunohystochemical demonstration of fibrin and factor VIII deposition within the adventitial zone and, later in the course, also in the subendothelial zone of small hepatic venules. However, deposition of platelets within the hepatic venules has not been clearly identified, although VOD is often associated with thrombocytopenia[28] and refractoriness to platelet transfusions.[29] It is current opinion that the activation of coagulation system may follow an injury to venular and sinusoidal endothelium, as suggested by the observed modifications of von Willebrand factor and serum angiotensin converting enzyme.[15] On this ground, it has been suggested that therapeutical approach to VOD should be devoted to counterbalance the hemostatic alterations induced by the endothelial damage, and there is some encouraging reports from the prophylactic use of prostaglandin E1[30] and heparin[31] in BMT patients. Moreover, successful treatment of clinically established VOD has recently been obtained with recombinant tissue plasminogen activator (rtPA).[32-34]

In order to evaluate the occurrence of hemostatic alterations, and their possible correlation, if any, with thrombotic complications occurring in the early phase after BMT, in this study we have prospectively evaluated an unselected population of 29 consecutive BMT patients referred to our Unit, in whom a comprehensive laboratory approach to assess alterations of the coagulation and fibrinolitic system was applied.

The results of our analysis indicate that some abnormalities of the hemostatic system may be found in the early period following BMT,

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although they do not unequivocally support the occurrence of a prothrombotic state. In fact, although the decrease of protein C and factor VIIAg levels might be the result of an intravascular consumption, this seems unlikely in view of the lack of any significant increase of F 1+2 levels. A decrease of natural anticoagulant levels has been observed also in other studies,[10-13; 15-16] and both protein S[10] and protein C[11] reduction was considered as predictive of VOD, while AT III (which has not been evaluated in this study) has never been associated with the development of VOD.[10-12,15,17,30] However, in a recent study, Catani et al.[17] failed to observe any significant decrease of protein C, protein S and antithrombin III, whereas they found elevated plasma levels of F 1+2 or TAT (thrombin-antithrombin) complexes suggestive of a prothrombic condition not apparently related to an impairment of natural anticoagulants. Whether these inconsistencies among different studies are related to different patient populations under study or to other unidentified factors still remain to be determined. We confirm in our patients, as in other series,[16,17] the presence of high fibrinogen levels, whose significance remains to be ascertained (the result of an acute phase reaction?). Similarly, the elevated levels of von Willebrand factor, which are believed to be the results of an endothelial damage, might as well be ascribed to an acute phase reaction. Finally, the possibility that low protein C and factor VIIAg levels are due to an impaired hepatic synthesis seems unlikely, in view of the normal protein S levels.

On the other hand, the decrease of plasminogen might as well suggest a stimulation of fibrinolytic processes, although we failed to detect any significant modification of either TPA, PAI-1 and D-dimer in support of this theory. These results are at variance with Catani et al.,[17] who found normal plasminogen levels in the presence of unmodified t-PA and PAI, and with Gordon et al.,[16] and Conlan et al.,[13] who reported low t-PA and PAI levels respectively.

Since elevated levels of tumor necrosis factor-alpha have been found in patients developing major complications following BMT, including VOD,[35] we sought to assess the modifications of this cytokine also in our patients. The findings of unmodified tumor necrosis factor-α in the absence of major early complications in our BMT patients are in accordance with these previous observations;[35] moreover, they suggest that macrophage release of tumor necrosis factor-alpha has little, if any, role in the pathogenesis of hemostatic alterations following BMT. In conclusion, we suggest that a complex pattern of hemostatic alterations takes place in the period immediately following BMT, although they may be clinically silent and not invariably associated with VOD or other thrombotic and/or hemorragic complications. Therefore, we cannot confirm others' observations[11,12,30] ascribing a predictive value to the decrease of either factor VII and protein C and S in patients who later developed VOD. The retrospective identification of N-terminal type III collagen in plasma of four patients who developed VOD[36] suggests that search for humoral markers of VOD is still worthwhile, but should be likely addressed at substances other than those involved in coagulation and hemostatic systems.

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