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PRETRANSPLANT FACTOR XII LEVELS CORRELATE WITH PROGNOSIS IN PATIENTS UNDERGOING AUTOLOGOUS GRAFT FOR HEMATOLOGICAL MALIGNANCIES

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ABSTRACT

A retrospective analysis of data collected in a previous study suggested that pre-conditioning levels of factor XII might have prognostic value in autologous graft recipients. In order to confirm whether pre-transplant factor XII (pFXII) levels could be correlated with outcome, seventy-six (35 autologous and 41 allogeneic) transplant recipients were prospectively evaluated. A significant direct relationship was found between pFXII levels and both overall and disease-free survival in the autologous grafts, but not in the allogeneic ones. Although the molecular mechanisms of this relationship still need to be clarified, these data seem to justify larger efforts to confirm whether factor XII (FXII) assay should be used in pre-transplant evaluation of patients.
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Key words: factor XII, BMT, hematologic malignancy

A number of prognostic factors for BMT patients have been recognized in several studies, such as stage and type of disease, age of the recipients, clinical condition and possibly others; however, to our knowledge, very few papers have specifically addressed the identification of blood parameters associated with outcome.[1-3] In a pre-transplant assessment of hemostatic function in patients undergoing autologous transplantation,[4] we observed a prolonged pre-conditioning aPTT in patients who subsequently experienced a less favorable outcome. Retrospective analysis of these patients (Cinotti *et al*., unpublished data) excluded the presence of lupus anticoagulants and clarified that prolonged aPTT were associated with low FXII levels. These observations prompted us to prospectively evaluate whether FXII levels might be correlated with long-term outcome in patients undergoing either autologous or allogeneic transplantation.

Materials and Methods

Seventy-six consecutive patients receiving BMT (41 allogeneic and 35 autologous) in our unit from April 1991 to July 1995 were included in the study. Patient characteristics are reported in Table 1. For the evaluation of hemostatic parameters, blood was drawn the day before the conditioning regimen was started (basal value). Plasma factor XII was measured by one-stage assay.[5] The coefficient of variation of FXII assay for repeated measurements on identical samples on different days was 10 to 15%, with an intra-assay variation of 3 to 5%. Fifty age- and sex-matched voluntary blood donors served as controls. None of the patients suffered from diffuse intravascular coagulation (DIC) or severe hepatic impairment at the time of pFXII evaluation. Patient characteristics were compared using the chi-square test, Mann Whitney U-test or Kruskal-Wallis analysis of variance when appropriate. Survival and disease-free survival were measured according to the method of Kaplan and Meier from the first day of the conditioning regimen to the date of the last follow up, documented relapse or death (deaths from all causes were included in estimates of survival). Cox regression was used to analyze the association between covariates and death or relapse. An arbitrary cutoff value of 86 U/dL was found to discriminate best between groups.

Results

Thirty-five autologous graft recipients were observed for a median period of 645 days, range 66-1578. During the follow up, 15 patients (42.8%) relapsed, 11 (31.4%) of whom died; all deaths followed, and were related to, relapse.

A survival analysis (Cox regression) revealed the existence of a relationship between pFXII levels and both overall survival (chi-square 6.24, $p = 0.012$) and disease-free survival (chi-square 9.12, $p = 0.002$). Choosing an arbitrary pF XII cutoff value of 86 U/dL, we found that patients who were below that level showed a relative risk of relapse of 11.91 (confidence limits: 2.41-24.67), and of 5.78 (confidence limits: 1.52-22.04) as regards death (Figure 1).

No relationship was found between FXII levels and cholinesterase assay, prothrombin time, type of malignancy, interval from diagnosis to transplant, number and type of chemotherapy regimens used prior to the transplant, type of conditioning regimen, or disease status prior to transplant. Of the 41 allogeneic transplant recipients followed for a median time of 463 days (range 53-1474), 1 graft

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Table 1. Characteristics of the 76 patients undergoing transplant.

Type of transplant	*Allogeneic*	*Autologous*
Age (yr)		
Median	38	37
Range	8-53	17-53
Male sex (%)	63	57
Diagnosis (no. of patients)		
NHL	6	7
AML	18	15
ALL	7	1
CML	8	3
HD		7
MM	2	2
Number of chemotherapy cycles prior to transplant		
Median	3	4
Range	1-12	2-25
Interval between diagnosis and BMT (days)		
Median	282	593
Range	2-2243	177-3111
Factor XII U/dL (mean ± sd)	93.7±27.8	112.0±51.2

NHL = non-Hodgkin lymphoma; LAM = acute myeloid leukemia; LAL = acute lymphocytic leukemia; CML = chronic myeloid leukemia; HD= Hodgkin's disease; MM = multiple myeloma.

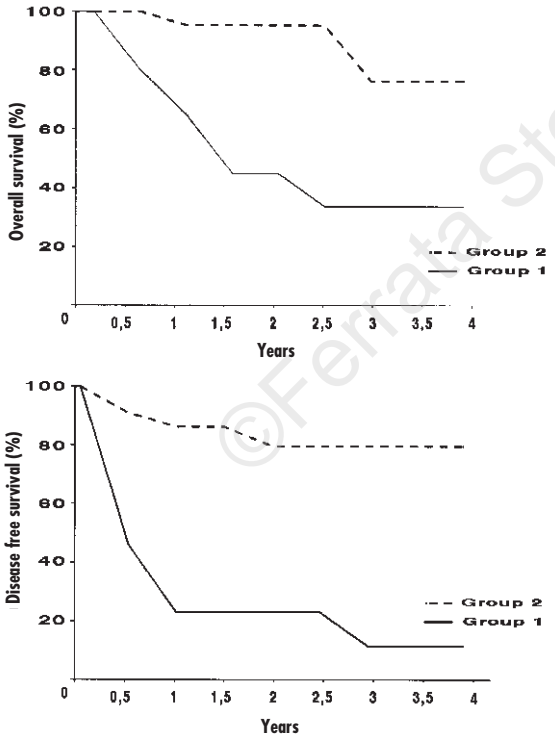

Figure 1. Overall survival (upper panel) and disease-free survival (lower panel) of 35 autologus graft recipients according to a basal FXII level > 86 U/dL (dashed line) or < 86 U/dL (continuous line).

failed, 3 (7.3%) suffered chronic GVHD, 14 (34.15%) relapsed, 21 (51.25%) died (4 of acute GVHD). No significant relationship was found between FXII and outcome.

Comment

In the present paper we show that a significant association exists between pFXII levels and prognosis in a group of 35 patients undergoing autologous graft for hematological malignancies. We failed to demonstrate the same association in a series of 41 allogeneic transplant recipients; whether this may be related to the size of the patient sample or to undefined biological differences between autologous and allogeneic BMT remains to be established.

Though we have a relatively thorough knowledge of the FXII structure,[6] its pathophysiological role is largely unexplored. Nevertheless, a large body of data indicate that complex relationships exist between FXII and various systems, such as coagulation, immunology, cytokines and hematopoiesis.[7-10] In conclusion, FXII could probably be viewed as a variable in some way influenced by a series of factors, among which the severity of the disease, the impact of disease and therapies on the patient, his or her immune status.

Though no convincing explanation of FXII behavior can be given, a pragmatic attitude would nonetheless suggest it is wise to perform this low-cost test prior to transplant, while waiting for advances in our knowledge capable of clarifying all the aspects of this matter.

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