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Hypofibrinogenemia in non-M3 acute myeloid leukemia. Incidence, clinical and laboratory characteristics and prognosis

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Among 379 patients with AML with FAB type M1, 2 and M4–7 diagnosed between 1978 and 1997 in our institution, 19 (5%) had hypofibrinogenemia (HF), ie a fibrinogen level <180 mg/dl. Compared to patients with normal fibrinogen (*n* = 360) patients with HF had significantly elevated markers of activation of coagulation (TAT, F1.2, FPA) and fibrinolysis (D-dimer, FDP) indicating that disseminated intravascular coagulation/ hyperfibrinolysis was the cause of hypofibrinogenemia. Patients with HF had significantly longer prothrombin times, thrombin clotting and reptilase times. Factor X and VIII were significantly lower than in patients without HF. With the exception of M7, HF occurred in all FAB subtypes, but was most common in M5 (12.1%). Patients with HF did not differ from those with normal fibrinogen with regard to age, sex, leukocyte count and other hematological parameters. During induction chemotherapy fibrinogen normalized rapidly (median 5 days) and there was no increased incidence of early hemorrhagic death. The overall and disease-free survival was similar to that of patients without HF.
Keywords: acute leukemia; hypofibrinogenemia; coagulation

Introduction

Hypofibrinogenemia due to disseminated intravascular coagulation (DIC)/hyperfibrinolysis is a common complication of acute promyelocytic leukemia (APL).[1–5] It was a frequent cause of serious bleeding before introduction of treatment with all-*trans* retinoic acid (ATRA). A coagulation disorder similar to that in APL may also occur in other FAB types of AML, but only a few data are available on the incidence in various FAB types, the risk of bleeding and the prognosis of these patients.[6,7]

We report on data of 379 patients with AML, seen in our institution between 1978 and 1997 in which coagulation studies were performed at diagnosis. We shall describe the clinical and laboratory characteristics of 19 patients with hypofibrinogenemia (fibrinogen level below 180 mg/dl) and compare them with 360 patients with normal fibrinogen (fibrinogen >180 mg/dl).

Materials and methods

Patients

Between 1978 and October 1997, 435 patients with the diagnosis of AML were admitted to our department. For this study the following patients were excluded: all patients with APL (*n* = 42) and patients in whom fibrinogen at diagnosis was not determined (*n* = 14).

Methods

AML were classified according to the FAB criteria. Immunophenotyping and cytogenetic analysis were done in most cases. The determination of PML-RAR alpha rearrangement was performed as previously described.[8]

Coagulation methods

Fibrinogen was determined according to Clauss.[9] Thrombin clotting time, thrombin time, partial thromboplastin time and reptilase time were performed according to standard procedures. The activity of clotting factors was determined by one-step clotting tests. Markers of coagulation and of fibrinolysis activation were determined by commercially available immunoassays: Fibrinopeptide A (radioimmunoassay; Imco, Byck-Mallinckrodt, Germany), thrombin–antithrombin complexes and prothrombin fragment F1+2 (ELISA, Behringwerke, Germany), d-dimer (ELISA, Stago, France). Fibrinogen–fibrin degradation products (FDP) were determined according to the method of Merskey *et al*.[10]

Statistical methods

Comparison of laboratory parameters between the two groups was done with the Mann–Whitney *U* test. Overall survival and disease-free survival was determined by the Kaplan–Meier method. Patients who underwent bone marrow transplantation were censored at the time of transplantation.

Results

Prevalence of hypofibrinogenemia in FAB subgroups

The overall prevalence of hypofibrinogenemia (HF) in non-M3 leukemias was 5.0% (19 of 379 patients). With the exception of M7, HF was observed in all FAB subtypes (Table 1). It was most common in patients with M5 (12.1%).

Clinical and laboratory characteristics of patients with hypofibrinogenemia

Table 2 shows that there was no significant difference between patients with and without HF regarding age, sex, leukocyte count, hemoglobin, platelet count and LDH at diagnosis.

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Table 1 Prevalence of hypofibrinogenemia (HF) according to FAB subtype

FAB	*Patients with HF (n)*	*Patients without HF (n)*	*Patients with HF (%)*
M0	1	12	7.7
M1	1	96	1.0
M2	4	95	4.0
M4	3	76	3.8
M5	8	58	12.1
M6	1	18	5.3
M7	0	9	0
various	1[a]	4	—
Total	19	360	5.0

[a]Patient with mast cell leukemia.

Karyotyping was successful in 10 patients. Six patients had a normal karyotype, two patients +8 and two a complex karyotype. PML-RAR alpha was negative in all patients tested (n = 5). The FAB subtypes of the patients where karyotyping or PML-RAR alpha was not available were as follows: M2 three patients, M4 two patients and M5 three patients.

Coagulation abnormalities

Patients with HF had a significantly prolonged prothrombin time (PT) and thrombin clotting time (TCT) (Table 2). Moreover, they had slightly but significantly lower factor II and a markedly lower factor X activity (Figure 1). There was no difference in factor V activity between both groups. Factor VIII activity was normal, but significantly lower than in patients without HF, in whom factor VIII activity was greatly increased (Figure 1). All patients with HF, in which these tests had been done, had markedly increased levels of coagulation (TAT, F1.2, FPA) and of fibrinolysis activation markers (D-dimer, FDP). The concentration of D-dimer, FPA, FDP (not shown), TAT and F1.2 was significantly higher in patients with HF compared to patients with a fibrinogen level above 180 mg/dl (Figure 2).

Effect of induction therapy on fibrinogen level

In all but two patients, the fibrinogen level became normal after induction chemotherapy treatment. The median time for normalization (fibrinogen above 180 mg/dl) without replacement treatment was 5 days (Figure 3). One of the two patients who did not normalize within 18 days died from cerebral hemorrhage at day 19 and the other was refractory to the first induction cycle, but his fibrinogen normalized after a successful second induction cycle.

Prognosis

Eleven (65%) out of 17 patients who had been treated with chemotherapy achieved a complete remission, four patients were resistant and two patients died during induction treatment (one of cerebral bleeding on day 19 after induction and the other from infection). The overall and the disease-free survival of patients with and without HF was not different (Figures 4 and 5).

Discussion

Infections and bleeding are the most common complications of induction therapy of acute myeloid leukemia.[3,11,12] The major reason for the bleeding tendency is the disease- and treatment-related thrombocytopenia. Hypofibrinogenemia is a well known and threatening complication of APL.[13,14] When patients with APL are treated with chemotherapy, the coagulation defect worsens during the initial phase of therapy.[5,15] As a result, fatal hemorrhages were quite common. Our data indicate that hypofibrinogenemia similar to that in APL may also occur in other types of acute myeloid leukemia. This observation has already been made in earlier studies which comprised, however, only a limited number of patients.[6,7] In our study which included a large number of unselected patients, we show that approximately 5% of patients with M1–2 and M4–7 have a reduced level of fibrinogen at diagnosis. This prevalence is slightly lower than that reported in two previous small studies. Zuazo *et al*[6] found a prevalence of 9.2% (5/54) and Nur *et al*[7] of 7.3% (3/41).

There is no universal agreement on how hypofibrinogene-

Table 2 Demographic, hematological and coagulation findings in non-M3 AML with or without hypofibrinogenemia (HF)

	Patients with HF (n = 19)				*Patients without HF (n = 360)*				*P value*
	n	*median*	*25% percentile*	*75% percentile*	*n*	*median*	*25% percentile*	*75% percentile*	
Sex (M/F)	10/9				180/180				
Age (years)	19	60	35	70	360	60	42	69	NS
Leukocytes (μl)	19	7400	3600	26600	360	12050	3500	46470	NS
Hemoglobin (g/dl)	19	9.5	8.8	11.0	360	9.3	8.0	10.6	NS
Platelets (/μl)	19	33000	15000	61000	360	45000	24000	80000	NS
LDH (U/l)	19	659	275	1196	345	405	266	708	NS
PT (%)	16	58	48	70	308	74	62	87	0.001
APTT (s)	17	36.1	31.3	39.5	324	34.8	32.0	38.9	NS
TCT (s)	19	15.0	14.7	18.5	303	14.3	13.4	15.4	0.003
RT (s)	13	15.4	15.0	19.2	187	17.2	15.6	20.0	NS

PT, prothrombin time; APTT, activated partial thromboplastin time; TCT, thrombin clotting time; RT, reptilase time.

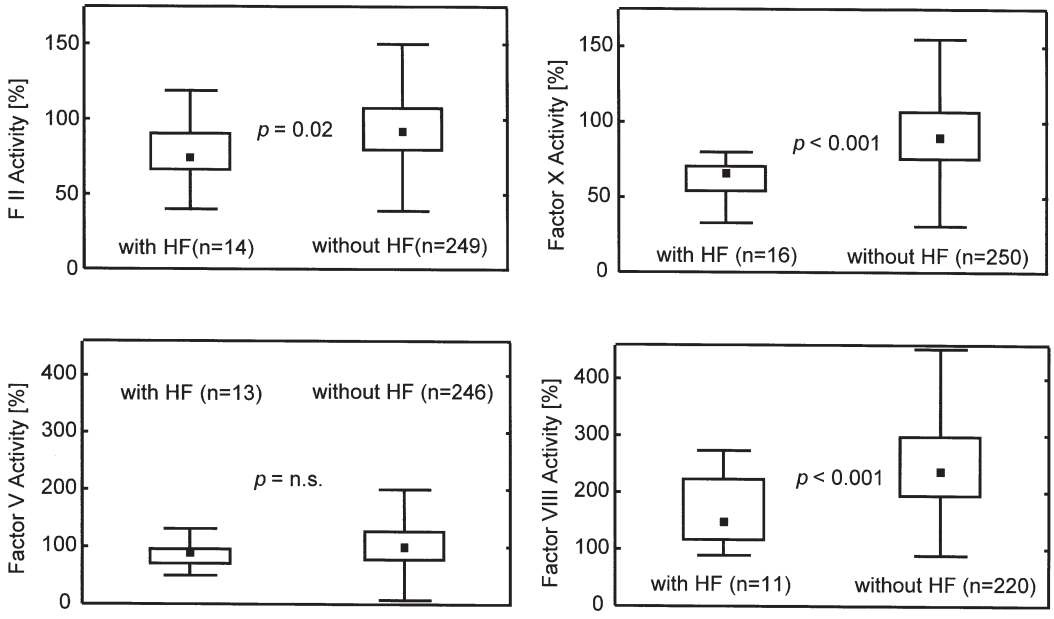

Figure 1 Box plots showing coagulation factors of non-M3 AML with or without hypofibrinogenemia at diagnosis. The square in the boxes shows the median, the bottom of the boxes marks the 25th percentile, the top of the boxes the 75th percentile. The bars mark the non-outlier range.

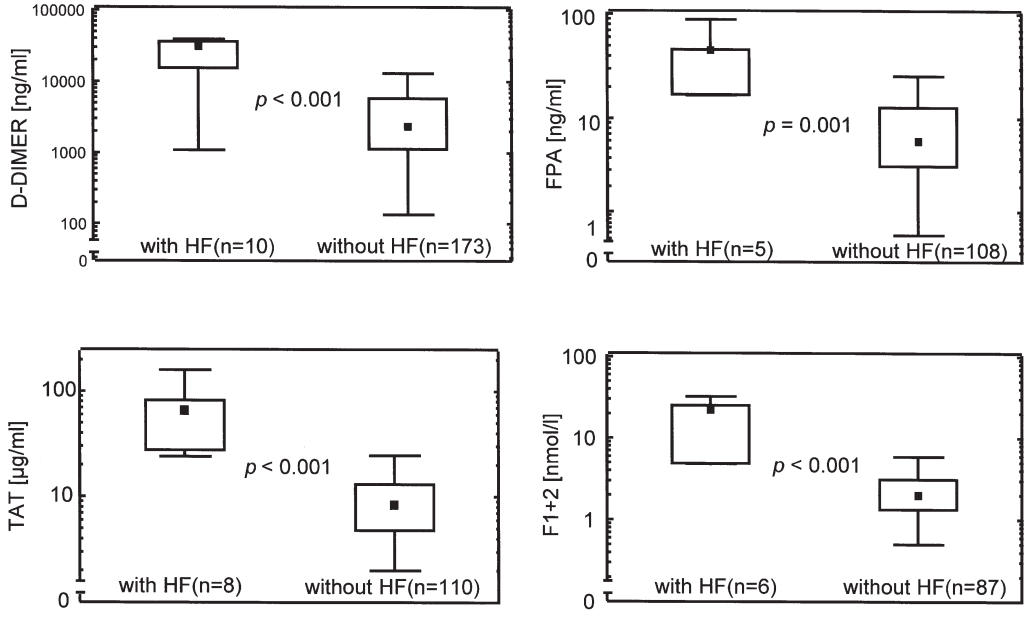

Figure 2 Box plots showing markers of coagulation and fibrinolysis activation in non-M3 AML with or without hypofibrinogenemia at diagnosis. The square in the boxes shows the median, the bottom of the boxes marks the 25th percentile, the top of the boxes the 75th percentile. The bars marks the non-outlier range.

mia should be defined in patients with AML. We have chosen a level of 180 mg/dl because this is the lower limit of the normal range in our laboratory. Others have used a cut-off level of 150 mg/dl or 200 mg/dl.[2,4,13] Most of our patients had fibrinogen levels well below 180 mg/dl. If we had chosen a cut-off level of 150 mg/dl the prevalence of hypofibrinogenemia would be only slightly less (4.5%).

The cause of hypofibrinogenemia in our patients was most likely DIC/hyperfibrinolysis. The level of activation markers of coagulation (FPA, TAT, F1.2) and of fibrinolysis (FDP, D-dimer) was markedly and significantly increased in comparison to AML patients with normal fibrinogen. During the time of this study, which extends over almost 20 years, the methods for the evaluation of activation of coagulation and fibrinolysis have changed (FPA and FDP in the earlier years and TAT, F1+2 and D-dimer during recent years).[16] Nevertheless, massive activation of the coagulation and fibrinolytic system could be documented in all cases. Therefore, we believe that the main reason for the low fibrinogen values was DIC/hyperfibrinolysis.

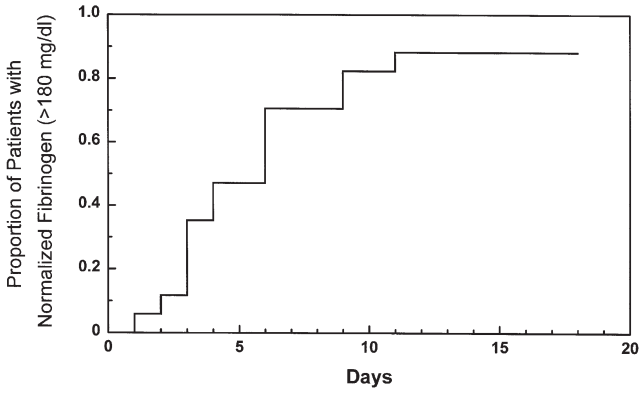

Figure 3 Proportion of patients with normalized fibrinogen over time after initiation of induction chemotherapy in non-M3 AML with hypofibrinogenemia (Kaplan–Meier method). The median time for normalization (fibrinogen above 180 mg/dl) without replacement treatment was 5 days.

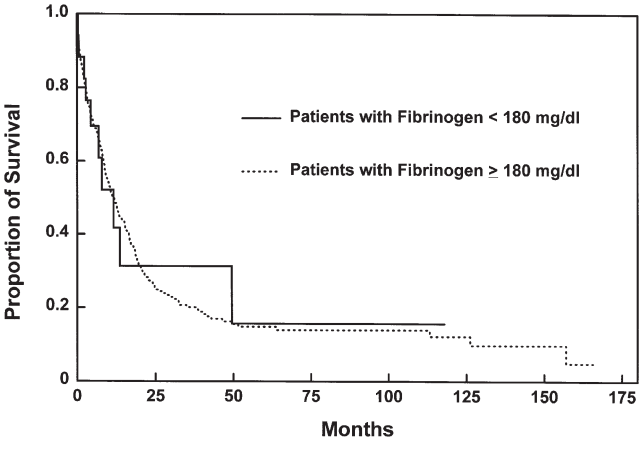

Figure 4 Overall survival of non-M3 AML with or without hypofibrinogenemia (Kaplan–Meier method). The difference in survival between the groups is statistically not significant.

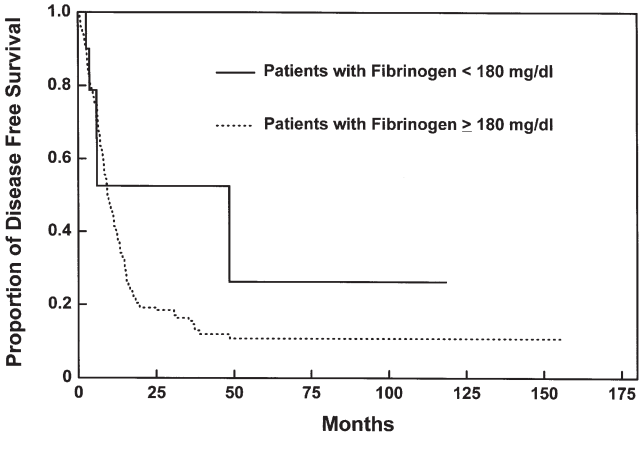

Figure 5 Disease-free survival of non-M3 AML with and without hypofibrinogenemia (Kaplan–Meier method). The disease-free survival was not different.

Among other coagulation abnormalities a modest, but highly significant decrease of factor X should be noted. This may be partly due to impairment of liver function,[17] but it may be also a specific effect since a reduction of other liver-synthesized clotting factors was either not present (factor V) or less pronounced (factor II). It has been shown by Falanga *et al*[18] that monoblasts contain a factor X-activating enzyme which could be responsible for this specific factor X deficiency. We have described a patient with a marked factor X deficiency and DIC in APL which was closely associated with the course of leukemia.[19] Factor V and VIII deficiencies have been described in patients with AML and DIC.[20] There was no deficiency of factor V and VIII in our cases; however, the DIC patients has a significantly lower factor VIII value compared to non-DIC patients.

In order to find out which features of the leukemia are associated with hypofibrinogenemia we made a number of comparisons. There was a clear-cut, significantly higher prevalence of HF in patients with monoblastic leukemia which was not unexpected and in agreement with earlier observations.[6,7] On the other hand, cases of HF were observed in all subtypes of AML except M7. Otherwise, there were no correlations to specific features of the leukemias. In particular, it was surprising that there was no correlation to the leukocyte count. Obviously, the occurrence of DIC is a specific feature of the leukemic cell and is not related to the tumor cell mass. When patients with APL and DIC were treated with chemotherapy alone (without ATRA) there was a high risk of early death (within 10 days) due to fatal bleeding. Rodeghiero *et al*[1] reported a 10% early hemorrhagic death rate in the GIMEMA studies. In contrast, no early death occurred in our non-M3 cases with HF, but one patient who remained hypofibrinogenic died from cerebral bleeding after day 10. This lower risk of fatal hemorrhage may be due to the fact that during chemotherapy fibrinogen recovered quickly (median time to normalization 5 days). In APL, the recovery of fibrinogen takes longer. Rodeghiero *et al*[1] found an unchanged fibrinogen value within 5 days of treatment and only a slight increase after 10 days.

A clinically important finding of our study is that the presence of DIC/hyperfibrinolysis with hypofibrinogenemia is not an adverse prognostic factor. The CR rate and the overall survival of these patients was not inferior to patients with normal fibrinogen. This is in contrast to patients with solid tumor and DIC/hyperfibrinolysis who have a very poor prognosis with no chance of cure.

In summary, it can be concluded from this study that: (1) DIC/hyperfibrinolysis with hypofibrinogenemia occurs in about 5% of non-M3 leukemias; (2) is most common in monoblastic leukemia; (3) resolves quickly during chemotherapy; (4) is not associated with the risk of early hemorrhagic death; and (5) is not a poor prognostic factor.

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