Early Deaths and Anti-Hemorrhagic Treatments in Acute Promyelocytic Leukemia. A GIMEMA Retrospective Study in 268 Consecutive Patients

By Francesco Rodeghiero, Giuseppe Avvisati, Giancarlo Castaman, Tiziano Barbui, and Franco Mandelli

The records of 268 consecutive patients with acute hypergranular promyelocytic leukemia, treated at 29 Italian centers between January 1984 and December 1987, have been reviewed to assess the incidence of early hemorrhagic deaths and the effectiveness of various anti-hemorrhagic treatments. Three separate groups were considered: 94 patients were treated with heparin, 67 with anti-fibrinolytics (tranexamic acid, ϵ-aminocaproic acid, or aprotinin), and 107 with supportive therapy alone. The overall incidence of early hemorrhagic death (within the first 10 days of treatment) was 9.4%, with no significant differences between the various groups. Similarly, there were no differences in complete remission rates or duration of survival. The consumption of packed red blood cells and platelet concentrates was similar for two of the groups, and there was a significantly greater use of platelet concentrates for heparin-treated patients. High blast cell counts on the day of admission were significantly associated with hemorrhagic death within the first 10 days. These counts, plus high blast cell counts and low platelet counts, were associated with death within 24 hours.

ACUTE PROMYELOCYTIC leukemia (APL) is a peculiar subtype of acute myelogenous leukemia frequently associated with clotting abnormalities and severe hemorrhagic diathesis.[1-8] Patients with APL can live for a long time if they survive hemorrhagic complications and achieve complete remission.[9]

Since the early 1970s, clotting abnormalities of APL have been ascribed to disseminated intravascular coagulation triggered by the release of procoagulant substances from leukemic cells,[10,11] and it seemed logical to propose heparin to control intravascular clotting and the subsequent consumption of hemostatic factors.[2-4,12,13] However, the beneficial effect of heparin has never been proved by prospective randomized trials, and its use, although suggested by standard textbooks,[14,15] is still supported only by the very limited evidence gained from analysis of small retrospective studies.[13,16,17] Uncertainties as to the best treatment of coagulopathy in APL are also reflected in anecdotal reports claiming beneficial effects of anti-fibrinolytic treatment alone[18,19] or in association with heparin,[20] on the basis of the purported capacity of tranexamic acid or ϵ-aminocaproic acid to control the hyperactive fibrinolysis found in these patients by some investigators.[18,21-23]

Recently, Goldberg et al[24] showed in a small group of patients that the coagulopathy associated with APL can be successfully managed with the currently available more intensive blood product support without using heparin. Furthermore, these investigators noted that in several studies the beneficial effects of heparin were demonstrated in comparison with historical series, thus failing to take into account both the more intensive chemotherapy made available in recent years and the increased availability of blood products. To avoid this bias, Hoyle et al[25] analyzed a retrospective series in which the heparin and the control groups were treated during the same period with comparable chemotherapy and supportive therapy, and, in contrast to Goldberg et al,[24] found a significant reduction of hemorrhagic deaths and a higher remission rate in heparin-treated patients.

In this study, data on consecutive patients diagnosed between 1984 and 1987 were collected within the framework of the GIMEMA group (Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto) from 29 centers representing almost all the Italian centers dealing with the treatment of acute leukemia. Any decision concerning the institution of a specific anti-hemorrhagic treatment (heparin, anti-fibrinolytic agents, or supportive treatment alone) was left to the discretion of the responsible physician.

During the study period, platelet concentrates, fresh frozen plasma, and packed red blood cells (RBCs) were easily available at all centers. Comparable anthracycline-containing chemotherapy was used for all patients.

MATERIALS AND METHODS

Patient data. A total of 282 consecutive patients were collected from 29 centers during the period from January 1984 to December 1987. APL was diagnosed according to French-American-British (FAB) criteria.[26] Only the hypergranular type (more than 90% of cases of APL diagnosed during this period) was considered. Hemorrhagic symptoms were divided into major (cerebral bleeding, macrohematuria, gastrointestinal bleeding, menorrhagia, hemoptysis) and minor (epistaxis, gum bleeding, micro-hematuria, petechiae or ecchymoses, hematomas). Data was recorded that concerned the interval between admission and insitution of chemotherapy; hemoglobin, blast count, platelet count, fibrinogen, and FDP (fibrinogen-fibrin degradation products) from admission to 10 days after starting induction therapy; and the type and quantity of supportive treatment (fresh frozen plasma, packed RBCs, whole blood, single- or multiple-donor platelet concentrates, cryoprecipitate). Although there was no written protocol for supportive treatment, a consensus policy, agreed on by all treating physicians, implied platelet transfusion to maintain platelet count (performed at least once a day) above 30,000/μL and plasma infusion to maintain fibrinogen above 100 mg/dL (fibrinogen tested every 1 to 3 days). Packed RBCs were administered to maintain hemoglobin above 8.5 g/dL.

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Table 1. Patient Outcome by Anti-Hemorrhagic Treatment

	Heparin N = 94 (35.1%) (%)	Supportive Treatment N = 107 (39.9%) (%)	Anti-Fibrinolytic N = 67 (25%) (%)
CR	58 (61.7)	66 (61.7)	43 (64.2)
Failure	13 (13.8)	14 (13.1)	6 (8.9)
Early hemorrhagic deaths	9 (9.6)	11 (10.3)	5 (7.5)
Early death from other causes	3 (3.2)	4 (3.7)	2 (3.0)
Late deaths	11 (11.7)	12 (11.2)	11 (16.4)

Anti-hemorrhagic treatments. Patients were divided into three groups on the basis of the different anti-hemorrhagic treatments: supportive therapy alone, heparin, or anti-fibrinolytic therapy. Five patients who died shortly after admission before any chemotherapy or anti-hemorrhagic treatment was instituted, and another nine patients who were administered both heparin and tranexamic acid, were excluded from analysis, leaving a total of 268 patients for evaluation.

A total of 107 patients were given only supportive therapy with platelet concentrates or/and fresh frozen plasma. Heparin was administered to 94 patients. Doses ranged from 2,500 (one case) to 37,500 U/d, starting before or in concomitance with institution of chemotherapy. For the lower doses, the subcutaneous route with calcium heparin was used. Anti-fibrinolytic treatment was given to 67 patients. Fifty-one patients were administered tranexamic acid (1.5 to 14 g/d, intravenously [IV]) or ε-aminocaproic acid (12 to 48 g/d, IV); infusion was started 1 to 3 days before chemotherapy for 26 patients, and at the same time as chemotherapy for the remaining cases, for a median period of 10 days. In addition, aprotinin (Trasylol, Bayer, Leverkusen, Germany), a serin protease inhibitor extracted from bovine lung that inhibited plasmin and conversion of plasminogen by its activators,[27] was administered to 16 patients for at least 8 to 10 days at doses of 800,000 to 2,000,000 U/d, IV.

For statistical purposes, the first 10 days of chemotherapy (days 1 to 10) were divided into two periods (days 1 to 5 and 6 to 10); the average platelet counts and fibrinogen concentrations, and the quantities of platelet concentrates or packed RBCs administered were calculated.

Early deaths were those occurring in the first 10 days after starting chemotherapy.

Chemotherapy. Daunorubicin monochemotherapy (2 mg/kg/d for 3 to 6 days) was administered to 131 patients. For the remaining cases, polychemotherapy consisting of doxorubicin (25 mg/m^2) or daunorubicin (50 mg/m^2), days 1 to 3, plus cytosine arabinoside (100 mg/m^2, twice daily for 7 to 10 days) and/or 6-thioguanine (100 mg/m^2, twice daily for 7 days) or VP-16 (100 mg/m^2, days 4 to 7) was administered. Complete remission (CR) and its duration were registered as reported by each center. Consolidation treatment consisted of further courses of intensive polychemotherapy; usually no maintenance treatment was administered.

Statistical analysis. Analysis of variance was used for comparison of different groups. Comparisons of outcomes within subgroups, in terms of complete remission rates and incidence of hemorrhagic deaths, were done by chi-squared tests. Survival curves (Kaplan-Meier method) were compared by the log rank test.

RESULTS

A total of 268 patients were evaluated. Ages ranged from 7 to 78 years, with a median of 41 years. Mean hemoglobin was 9.3 g/dL (range 3 to 16), median blast count was 1,100/μL (range 0 to 300,000), and mean platelet count 38,540/μL (range 1,000 to 284,000).

The overall remission rate was 62% (167 of 268). A total of 85 of 126 (67%) patients treated with daunorubicin alone and 82 of 142 (58%) treated with polychemotherapy entered CR (P not significant). The rate of early hemorrhagic death was the same in the two groups: 12 of 126 (10%) versus 13 of 142 (9%); P not significant.

Among 34 patients who died within the first 10 days of treatment (early deaths), 25 of 34 (74%) died from hemorrhage: 3 gastrointestinal and the remaining cerebral hemorrhages, confirmed in 5 cases by computed tomography and in 2 cases by autopsy. The other 9 patients died of other causes: 3 of sepsis, 2 of acute pulmonary edema, 2 of cardiac arrest, 1 of acute myocardial infarction (in a patient treated with supportive therapy alone), and 1 of respiratory distress syndrome. The majority of patients died during the first 5 days (23 of 34; 68%); 18 of 23 (78%) from bleeding.

A total of 34 patients died after the first 10 days of treatment and before ascertainment of remission. Twelve died of hemorrhage (mainly intracranial), 16 of infections, 2 of acute renal failure, 1 of intestinal perforation, 1 of acute liver failure, 1 of myocardial infarction, and 1 of massive pulmonary embolism (both of these patients were given supportive care alone).

Of the several pretreatment characteristics of our patients, only high blast cell counts (greater than 10,000/μL) were found to be significantly related adversely to the incidence of early hemorrhage ($P = .002$). Nearly significant P values were observed for low platelet counts (less than 10,000/μL), increased FDP (greater than 40 μg/mL), and short time

Table 2. Distribution of Possible Risk Factors for Early Hemorrhage in the Three Groups of Patients

	Heparin N = 94 (%)	Supportive Treatment N = 107 (%)	Anti-Fibrinolytic N = 67 (%)
Age (yrs)*			
<50	75 (80)	67 (63)	45 (67)
≥50	19 (20)	40 (37)	22 (33)
Platelets†			
<30,000/μL	58 (62)	47 (44)	38 (57)
≥30,000/μL	36 (38)	60 (56)	29 (43)
Blasts/μL			
<1,000	42 (45)	51 (48)	37 (55)
≥1,000	52 (55)	56 (52)	30 (45)
Hemoglobin			
<11 g/dL	73 (78)	88 (82)	55 (82)
≥11 g/dL	21 (22)	19 (18)	12 (18)

*$P = .026$ between groups.

†$P = .04$ between groups.

Table 3. Stratification of Patients Treated With Heparin by the Different Doses

Dosage (U/24 h)	Patients (%)	Dosage (median)	Days of Treatment (median)	Hemorrhagic Deaths	CR (%)
<10,000	11 (12)	7,500	9	0	9 (82)
≥10,000 ≤ 15,000	54 (57)	10,000	9	4	35 (65)
>15,000	29 (31)	20,000	7	5	14 (48)

intervals from admission to start of chemotherapy (less than 12 hours). For the rate of CR, male sex, older age (greater than 40 years), and increased FDP (greater than 40 μg/mL) showed significant relationships ($P < .05$), whereas high blast cell counts did not. Platelet counts, FDP, and fibrinogen levels were analyzed in patients with and without major hemorrhagic symptoms. Only fibrinogen was significantly lower (125 mg/dL *v* 160 mg/dL; $P < .02$) in patients with more severe hemorrhagic pictures.

Table 1 reports the clinical outcomes for the patients in relationship to the different anti-hemorrhagic treatments. It is evident that neither heparin nor anti-fibrinolytic treatments influenced the rate of early deaths or CR. Considering the patients treated with aprotinin separately did not change the statistical outcome.

Comparability of the three groups of patients was assessed by analyzing the distribution of the parameters that proved to be predictive for early hemorrhages in a previous series of patients[17] (Table 2). The heparin group included more patients younger than 50 years and a higher proportion of subjects with less than 30,000 platelets/μL (Table 2). However, the clinical outcome did not change after stratifying for age and platelet count. Furthermore, the effectiveness of anti-hemorrhagic treatments was also calculated separately for high-risk patients selected according to the criteria of Kantarjian et al[17] or according to the different heparin doses (Table 3), but again no statistically significant differences emerged.

The only difference in fibrinogen level or platelet count in the various treatment groups was a significantly lower platelet count during days 1 to 5 in the heparin group ($P < .0005$) (Table 4). Increases in fibrinogen were observed in all groups toward the end of induction therapy, whereas the platelet count remained substantially unchanged.

Platelet concentrate consumption was significantly greater ($P < .01$) in the heparin group than the other groups (Table 5). Sixty-three patients were administered fresh frozen plasma during the first 10 days. Of these, 40 (63%) entered CR, in comparison with 127 of 205 (62%) not infused with plasma (*P* not significant).

To explore the predictive value of biologic parameters as measured on the day of death, we obtained a control group by computerized sorting. Patients who died from hemorrhage in days 0 to 10 (cases) were coupled with an equal number of patients who were alive or died from other causes on the corresponding day (controls). After checking that age, sex, and missing data were similarly distributed in cases and controls, the two groups were compared by the chi-squared test. Hemoglobin and fibrinogen levels on the day of death were not predictive of subsequent hemorrhagic death as they were not when measured at time of diagnosis, whereas high blast counts (greater than 10,000/μL) and low platelet counts (≤10,000/μL) were confirmed to be significantly predictive ($P < .004$ and $<.05$).

The median survival in months was 12.5 for all patients, 11.5 for the heparin group, 10 for the anti-fibrinolytic group, and 14 for the group treated with supportive therapy alone. These differences were not significant.

DISCUSSION

Our study differs from previous reports in several ways. This is the first multicenter study in which only patients gathered consecutively were admitted. Limiting the period of study to patients diagnosed from 1984 to 1987 further avoided the bias of comparison of patients administered different supportive treatment or chemotherapy. For the majority of patients laboratory data were available not only at admission but also during induction, enabling us to perform a detailed analysis of risk factors as modified by chemotherapy. Finally, a group of patients was treated solely with anti-fibrinolytic agents, allowing for the first time an analysis of the effects of this treatment in a large group of patients.

The principal characteristics of our patients (age, sex, and hemoglobin; blast cells and platelet count at admission) were not different from those in other reported series of

Table 4. Mean Fibrinogen Levels and Platelet Counts in the Different Treatment Groups at Diagnosis and During the 10 Days After Starting Chemotherapy

	Heparin		Supportive Treatment		Anti-Fibrinolytic	
	Mean	SD	Mean	SD	Mean	SD
Fibrinogen (mg/dL)						
Diagnosis	149.8	107.3	182.7	138.3	148.2	105.5
1-5	153	83.1	151.8	95.9	146.9	95.3
6-10	225.8	98.8	195.9	106.1	173.4	105.4
Platelet ($\times 10^3/\mu L$)						
Diagnosis	32.7	32.1	44.8	37.4	37.1	39.9
1-5*	30.1	20.0	47.4	32.1	38.6	28.8
6-10	33.8	19.6	45.5	29.8	34.6	24.6

*Platelet count during 1-5 significantly lower in heparin group ($P < .0005$).

Table 5. Supportive Treatment During Induction Therapy in the Different Treatment Groups

Patients	Units of Platelet Concentrates Mean (SD)	Units of Packed RBCs Mean (SD)
Heparin*	61.9 (41.9)	5.5 (2.8)
Supportive treatment	49.6 (36.5)	5.7 (3.5)
Anti-fibrinolytic	44.5 (30.7)	4.5 (2.5)

*The platelet concentrate consumption was significantly greater in the heparin-treated group than other groups ($P < .01$).

APL.[13,16,17,25,28-30] In detail, the majority of cases had laboratory pictures consisting of low fibrinogen levels (145 of 268, 54%, ≤150 mg/dL), increased FDP (177 of 232, 76%, ≥40 μg/dL), or both (110 of 232, 47%). The average platelet count was lower than that usually found in other types of acute myelogenous leukemia.[31] The overall remission rate was 62%, very similar to that reported by other investigators.[17,25,28,30,32,33]

We were not able to demonstrate any beneficial effects of heparin or anti-fibrinolytic agents in reducing the incidence of early deaths, or in improving CR rate or long-term survival. The patients treated with heparin were younger and included a larger proportion of subjects with fewer than 30,000 platelets/μL (Table 2), but comparison of the clinical outcome after stratifying patients according to age and platelet count did not show any significant differences. A wide range of heparin doses was used, but most patients were administered 150 to 300 U/kg/d. In the majority of cases this treatment was started at the onset of chemotherapy and stopped when there was amelioration of the fibrinogen level or disappearance of blast cells from peripheral blood (median treatment, 9 days). The significantly larger amount of platelet concentrates used by the heparin-treated group (Table 5), but not resulting in higher average platelet counts (Table 4), might partially be accounted for by direct effects of heparin on the platelet count[34] or by the presence of a more severe bleeding tendency in this group. In the study of Hoyle et al,[25] patients treated with heparin did significantly better due to the strikingly lower incidence of hemorrhagic deaths during the first week. It should be emphasized that in that study 25% of the patients not receiving heparin died of hemorrhage during the first week, in comparison with less than 10% in our study. Thus, it seems reasonable that the different supportive treatment might be responsible for this discrepancy. Furthermore, the hemorrhagic death rate for heparin-treated patients in our study was very similar to that found by Hoyle et al.[25]

We were not able to find any significant reduction of hemorrhagic deaths or increased survival in association with the use of anti-fibrinolytic agents (Table 1). However, it is noteworthy that we have seen no thrombotic manifestations. Recent data reported by Avvisati et al[35] from a small, double-blind randomized study limiting the administration of tranexamic acid to the first 6 days of chemotherapy demonstrate a reduction of packed RBCs and platelet requirements and of hemorrhagic symptoms, but the value of this treatment should be evaluated in a large prospective study.

At diagnosis, only high blast cell counts (greater than 10,000/μL) were predictive of early hemorrhagic death ($P < .002$), in agreement with the results of other studies.[17,25] Like Kantarjian et al,[17] we observed an association, although not significant, of increased incidence of early fatal hemorrhage with low platelet count ($P = .08$) and increased FDP ($P = .06$), whereas fibrinogen and hemoglobin levels were not significant as predictive variables in our patients; only high blast cell counts and low platelet counts were highly predictive of death within 24 hours ($P < .004$ and $< .05$). These results emphasize the clinical importance of rapid blast destruction and justify every attempt to maintain platelet levels in these patients.

In conclusion, although it is still well-established that an increased risk of hemorrhagic death is associated with APL, no definite prophylactic treatment with either heparin, aimed at controlling the ongoing intravascular thrombin generation occurring in this disease,[36-38] or with anti-fibrinolytic agents, aimed at reducing hyperactive fibrinolysis,[21-23] can be proposed on the basis of the literature surveyed or our present data. Only prospective randomized trials (not suffering from the limitations of the retrospective analyses available thus far) may, we hope, definitely clarify the most effective anti-hemorrhagic treatment for APL.

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Appendix. Contributing Centers

Institution	Investigators	Cases
Clin. Medica, Osp. Nuovo Torrette, Ancona	P. Leoni, M. Montillo	5
Serv. Ematologia, Osp. Civ., Avellino	E. Volpe, F. Palmieri	6
Serv. Ematologia, Università Bari	V. Liso, G. Specchia	17
Div. Ematologia, Ospedali Riuniti, Bergamo	T. Barbui, A. Falanga	21
Ist. Ematologia, Osp. "S. Orsola," Bologna	S. Tura, L. Gugliotta	14
Serv. Ematologia, Bolzano	P. Coser	2
Div. Ematologia, Osp. "A. Businco," Cagliari	G. Broccia	13
Div. Ematologia, Università Ferrara	G. Castoldi	8
Div. Ematologia, Università Firenze	G. Rossi Ferrini, S. Ciolli	6
Div. Ematologia, Osp. "S. M. Goretti," Latina	L. Deriu, A. Chierichini	10
Sez. Ematologia, Osp. Niguarda, Milano	F. Baudo	7
Div. Ematologia, Osp. Civ., Monza	E. Pogliani	12

(Continued on following page)

Appendix. Contributing Centers (Cont'd)

Institution	Investigators	Cases
Sez. Aut. Ematologia, N. Policlinico, Napoli	B. Rotoli	4
Div. Ematologia, Osp. N. Pellegrini, Napoli	R. de Biasi	5
Sez. Aut. TERE, Osp. "Cardarelli," Napoli	R. Cimino, C. De Rosa	3
Div. Ematologia, Policlinico, Palermo	M. Tamponi Reyes	5
Clin. Medica, Policlinico, Palermo	A. Cajozzo	2
Div. Ematologia, Università Parma	V. Rizzoli, G. Degliantoni	5
Div. Ematologia, Policlinico, Pavia	C. Bernasconi, M. Lazzarino	27
Clin. Medica II, Policlinico, Pavia	E. Ascari	11
Div. Ematologia, Osp. Civ., Pescara	G. Torlontano, A. Spadano	3
Sez. Ematologia, Osp. "San Carlo," Potenza	F. Ricciuti	2
Sez. Ematologia, Univ. "La Sapienza," Roma	F. Mandelli, G. Avvisati	27
Div. Ematologia, Univ. Cattolica, Roma	B. Bizzi, G. Leone	11
Div. Ematologia, S. Giovanni Rotondo	M. Carotenuto	7
Ist. Ematologia, Università Sassari	M. Longinotti	1
Div. Medica, Osp. "San Giovanni," Torino	L. Resegotti	14
Div. Ematologia, Università Verona	G. Perona, V. Meneghini	9
Div. Ematologia, Osp. "San Bortolo," Vicenza	E. Dini, F. Rodeghiero, G. Castaman	25

REFERENCES

1. Hillestad LK: Acute promyelocytic leukemia. Acta Med Scand 49:189, 1957
2. Didisheim P, Trombold JS, Vandervoort RLE, Sougin Mibashan R: Acute promyelocytic leukemia with fibrinogen and factor V deficiencies. Blood 23:717, 1964
3. Gralnick HR, Bagley J, Abrell E: Heparin treatment for the hemorrhagic diathesis of acute promyelocytic leukemia. Am J Med 52:167, 1972
4. Bernard J, Weil M, Boiron M, Jacquillat C, Flandrin G, Gemon MF: Acute promyelocytic leukemia: Results of treatment by daunorubicin. Blood 41:489, 1973
5. Rodeghiero F, Barbui T, Battista R, Chisesi T, Rigoni G, Dini E: Molecular subunits and transamidase activity of factor XIII during disseminated intravascular coagulation in acute leukemia. Thromb Haemostas 43:6, 1980
6. Rodeghiero F, Mannucci PM, Viganò S, Barbui T, Gugliotta L, Cortellaro M, Dini E: Liver dysfunction rather than intravascular coagulation as the main cause of low protein C and antithrombin III in acute leukemia. Blood 63:965, 1984
7. Bauer KA, Rosenberg R: Thrombin generation in acute promyelocytic leukemia. Blood 64:791, 1984
8. Rodeghiero F, Barbui T, Dal Belin Peruffo A, Dini E: Defective fibrin cross-linking in acute leukemia. Thromb Haemostas 52:343, 1984
9. Cunningham I, Gee TS, Reich LM, Kempin SJ, Naval AN, Clarkson BD: Acute promyelocytic leukemia: Treatment results during a decade at Memorial Hospital. Blood 73:1116, 1989
10. Gralnick HR, Abrell E: Studies of the procoagulant and fibrinolytic activity of promyelocytes in acute promyelocytic leukemia. Br J Haematol 24:89, 1973
11. Gouault-Heilmann M, Chardon E, Sultan C, Josso F: The procoagulant factor of leukaemic cells: Demonstration of immunologic cross-reactivity with human brain tissue factor. Br J Haematol 30:151, 1975
12. Baker W, Bang NU, Nachman RL, Raafat R, Horowitz HI: Hypofibrinogenemic hemorrhage in acute myelogenous leukemia treated with heparin. Ann Intern Med 61:116, 1964
13. Drapkin RL, Gee TS, Dowling MD, Arlin Z, McKenzie S, Kempin S, Clarkson B: Prophylactic heparin therapy in acute promyelocytic leukemia. Cancer 41:2484, 1978
14. Wintrobe MM, Lee GR, Boggs DR, Birhell TC, Roerster J, Athens JW, Lukens JN (eds): Clinical Hematology, Philadelphia, PA, Lea & Febiger, 1981, p 1226
15. Williams WJ, Beutler E, Erslev AJ, Lichtman MA (eds): Hematology. New York, NY, McGraw-Hill, 1983, p 239
16. Cordonnier C, Vernant JP, Brun B, Gouault-Heilmann M, Kuentz M, Bierling P, Farcet JP, Rodet M, Duedari N, Imbert M, Jouault H, Mannoni P, Reyes F, Dreyfus B, Rochant H: Acute promyelocytic leukemia in 57 previously untreated patients. Cancer 55:18, 1985
17. Kantarjian HM, Keating MJ, Walters RS, Estey EH, McCredie KB, Smith T, Dalton W, Cork A, Trujillo JM, Freireich EJ: Acute promyelocytic leukemia. M.D. Anderson Hospital experience. Am J Med 80:789, 1986
18. Keane TJ, Gorman AM, O'Connell LG, Fennelly JJ: Epsilon-aminocaproic acid in the management of acute promyelocytic leukemia. Acta Haematol 56:202, 1976
19. Chan TK, Chan GTC, Chan Y: Hypofibrinogenemia due to increased fibrinolysis in two patients with acute promyelocytic leukemia. Aust N Z J Med 14:245, 1984
20. Schwartz BS, Williams EC, Conlan MG, Mosher DF: Epsilon-aminocaproic acid in the treatment of patients with acute promyelocytic leukemia and acquired α-2-plasmin inhibitor deficiency. Ann Intern Med 105:873, 1986
21. Rand JJ, Maloney WD, Sise HS: Coagulation defects in acute promyelocytic leukemia. Arch Intern Med 123:39, 1969
22. Bennet M, Parker AC, Ludlam CA: Platelet and fibrinogen survival in acute promyelocytic leukemia. Br Med J 2:565, 1976
23. Avvisati G, ten Cate JW, Sturk A, Lamping R, Petti MC, Mandelli F: Acquired α-2-antiplasmin deficiency in acute promyelocytic leukemia. Br J Haematol 70:43, 1988
24. Goldberg MA, Ginsburg D, Mayer RJ, Stone MR, Maguire M, Rosenthal DS, Antin JH: Is heparin administration necessary during induction chemotherapy for patients with acute promyelocytic leukemia? Blood 69:187, 1987
25. Hoyle CF, Swirsky DM, Freedman L, Hayhoe FGJ: Beneficial effect of heparin in the management of patients with APL. Br J Haematol 68:283, 1988
26. Bennet JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C: Proposal for the classification of the acute leukemias. Br J Haematol 33:451, 1976
27. Verstraete M: Haemostatic drug. A critical appraisal. The Hague, The Netherlands, Martinus Nijhoff, 1977
28. Ruggero D, Baccarani M, Guarini A: Acute promyelocytic leukemia: Results of therapy and analysis of 13 cases. Acta Haematol 58:108, 1977

29. Petti MC, Avvisati G, Amadori S, Baccarani M, Guarini AR, Papa G, Rosti GA, Tura S, Mandelli F: Acute promyelocytic leukemia: Clinical aspects and results of treatment in 62 patients. Haematologica 72:151, 1987

30. Sanz M, Jargue I, Martin G, Lorenzo I, Martinez J, Rafecas J, Pastor E, Sayas MJ, Sanz G, Gomis F: Acute promyelocytic leukemia. Therapy results and prognostic factors. Cancer 61:7, 1988

31. Rodeghiero F, Castaman G: Disseminated intravascular coagulation in acute leukemia, in Barbui T, Falanga A, Minetti B, Gorini S, Tognoni G, Donati MB (eds): Infections and Haemorrhage in Acute Leukaemia. London, UK, Libbey, 1989, p 45

32. Daly PA, Schiffer CA, Wiernik PH: Acute promyelocytic leukemia: Clinical management of 15 patients. Am J Hematol 8:347, 1980

33. McKenna RW, Parkin J, Bloomfield CD, Sundberg RD, Brunning RD: Acute promyelocytic leukemia: A study of 39 cases with identification of a hyperbasophilic macrogranular variant. Br J Haematol 50:201, 1982

34. Schwartz KA, Royer G, Kaufman DB, Penner JA: Complication of heparin administration in normal individuals. Am J Hematol 19:355, 1985

35. Avvisati G, ten Cate JW, Buller HR, Mandelli F: Tranexamic acid for control of haemorrhage in acute promyelocytic leukaemia. Lancet 2:122, 1989

36. Myers TJ, Rickles FR, Barb C, Cronlund M: Fibrinopeptide A in acute leukemia: Relationship of activation of blood coagulation to disease activity. Blood 57:518, 1981

37. Gugliotta L, Viganò S, D'Angelo A, Guarini A, Tura S, Mannucci PM: High fibrinopeptide A (FPA) levels in acute non-lymphocytic leukemia are reduced by heparin administration. Thromb Haemost 52:301, 1984

38. Rodeghiero F, Castaman G, Soffiati G, Quaglio R, Castronovo S, Cortesi S, Dini E: Clinical significance of fibrinopeptide A in acute lymphocytic and non-lymphocytic leukaemia. Blut 59:177, 1989