Chronic Myelomonocytic Leukemia According to FAB Classification: Analysis of 35 Cases

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Thirty-five patients who fulfilled the FAB diagnosis criteria of chronic myelomonocytic leukemia (CMML), i.e., myelodysplastic features, monocytosis over 10^9/liter, bone marrow monocyte infiltration, blast cells <5% in the peripheral blood and <30% in the bone marrow, are analyzed. CMML appears as an entity distinct from myelodysplastic and myeloproliferative disorders. Splenomegaly, anemia, thrombocytopenia, leukocytosis with monocytes and granulocytic cells in all stages of development, increased blood and urine lysozyme levels without renal failure, and polyclonal hyperimmunoglobulinemia are its main clinical and biologic features. With conventional cytotoxic drugs (6-mercaptopurine, hydroxyurea), the prognosis of CMML appears poor (median survival 475 days). None of the clinical hematologic or biologic parameters tested had a significant effect on prognosis. As other chemotherapy trials seemed necessary, we recently administered small doses of cytosine-arabinoside (ARA-C) to six patients over several consecutive days and obtained a complete remission in four. These preliminary results must be confirmed by larger series using the diagnostic criteria proposed by the FAB cooperative group.

THE GRANULOCYTIC-MONOCYTIC myeloid cell series is believed to arise from a common committed stem cell.[1] Therefore, a leukemic proliferation may have both granulocytic and monocytic differentiation patterns, either as an acute leukemia (acute myelomonocytic leukemia, M4 in FAB classification)[2] or a chronic process. Chronic myelomonocytic leukemia (CMML) appears to be an overlap of various disorders, as it shows features of both myeloproliferative and myelodysplastic syndromes, with the result that, in addition to the CMML appellation, many similar cases have been reported under various names: preleukemic syndrome,[3] erythromonocytic leukemia,[4] chronic monocytic leukemia,[5] and subacute myelomonocytic leukemia.[6,8]

Recently, after reviewing the blood and bone marrow films of a large number of patients, the FAB cooperative group decided to include CMML in the larger group of myelodysplastic syndromes and to define diagnostic criteria.[9] We present the clinical and biologic findings and the course of 35 patients fulfilling all of these criteria. Our results confirm that CMML has distinctive hematologic features and evolution justifying its separation from other myeloproliferative and myelodysplastic disorders. Some features are emphasized, such as associated immune abnormalities, the absence of severe renal disturbances despite high levels of urinary lysozyme, and the sensitivity of WBC and platelet counts to moderate doses of cytotoxic drugs, and some apparently new therapeutic approaches are discussed.

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MATERIALS AND METHODS

Patient Population

We studied 35 cases of CMML admitted to our department from 1975 to 1981. The diagnosis of CMML was established according to the FAB cooperative group criteria,[9] i.e., dyspoietic features of myelodysplastic syndromes associated with a blood monocytosis over 10^9/liter, an increase in bone marrow monocyte precursors, and a blast cell percentage less than 5% in the peripheral blood and less than 30% of nucleated cells in the bone marrow.

Hematologic and Immunologic Data

Bone marrow (BM) biopsies were studied according to previously described methods.[10] The extent and importance of bone marrow fibrosis were appreciated with a Gordon-Sweet silver staining for reticulin fibers and a Masson trichrome staining for collagen fibers. Blood and urine lysozyme were measured by turbidimetry.[11] Bone marrow cytogenetic studies were performed with a standard "direct" technique. Serum immunoglobulins were investigated by Ouchterlony's radial immunodiffusion or nephelometry and immunoelectrophoresis. Immunohematologic tests included direct antiglobulin Coombs' test and elution of anti-RBC autoantibodies at 56°C, followed by agglutination tests at 37°, 22°, and 4°C. Cold agglutinin titers equal to or higher than 32 were considered significant.

Treatment

Four patients did not receive any antileukemic therapy: one because of an early death from cardiac failure, two because of severe thrombocytopenia, and one because of the slow evolution of the disease. Twenty-five patients were treated with hydroxyurea (from 1.5 g to 3.5 g/wk) and/or 6-mercaptopurine (from 300 to 700 mg/wk). Six patients were treated with 10 mg/sq m (range 15–20 mg) b.i.d. of cytosine-arabinoside (subcutaneous injections) for 21–25 consecutive days.

Statistical Procedures

All results are given as mean ± SE or median. The relationships between continuous parameters was studied using a descriptive

multivariate method, the principal component analysis.[12] Survival from date of diagnosis was estimated by the Kaplan-Meier method.[13] The prognostic value of each parameter was studied by the log-rank test.[14] In the case of continuous parameters, the variable was split into three classes. The Cox model[14] was used to take into account simultaneously several parameters, i.e., WBC, monocytosis, platelet counts, peripheral blood and bone marrow blast cells percentages, serum IgG levels, blood lysozyme levels. The variables were introduced into the model under their native expression.

RESULTS

Clinical Findings

There were 20 males and 15 females, with a mean age of 71.5 yr (range 49–84). None of the patients had a prior history of therapeutic or occupational exposure to potential carcinogenic agents. The mean time lapse between the onset of symptoms and diagnosis was 5.8 mo. The presenting symptoms and the signs at the time of diagnosis are shown in Table 1.

Hematologic Findings (Fig. 1)

Anemia was present in 31 cases (89%), with a mean hemoglobin level of 9.9 ± 0.3 g/dl. A high reticulocyte count was noted in 10 cases. The median WBC count was 11.5 × 10^9/liter (range 3.8–177 × 10^9/liter). The median monocytosis was 3.4 × 10^9/liter (range 1.2–84.5 × 10^9/liter). Less than 5% peripheral blast cells was noted in 12 patients, whereas myeloid precursors were present in the blood of 27 patients. Thrombocytopenia of less than 100 × 10^9/liter was noted in 18 cases and less than 50 × 10^9/liter in 6 cases. Median platelet count was 97 × 10^9/liter.

Table 1. Clinical Features of the 35 Cases at the Time of Diagnosis

Presenting symptoms	Cases	Percent
Anemia symptoms	17	48
Infection	7	20
Bleeding	6	17
Increasing spleen size	6	17
Fatigue	3	8
Fever without infection	2	5
Signs		
Karnofsky		
80–100	14	40
50–80	12	34
<40	9	26
Bleedings	17	48
Splenic enlargement*		
+	11	31
+ +	4	11
+ + +	4	11
Hepatomegaly	15	43
Enlarged lymph nodes	11	31
exceeding 2 cm in diameter	3	8

*Splenic enlargement: (+) lower tip less than 5 cm from the costal margin; (+ +) from 5 to 10 cm; (+ + +) more than 10 cm.

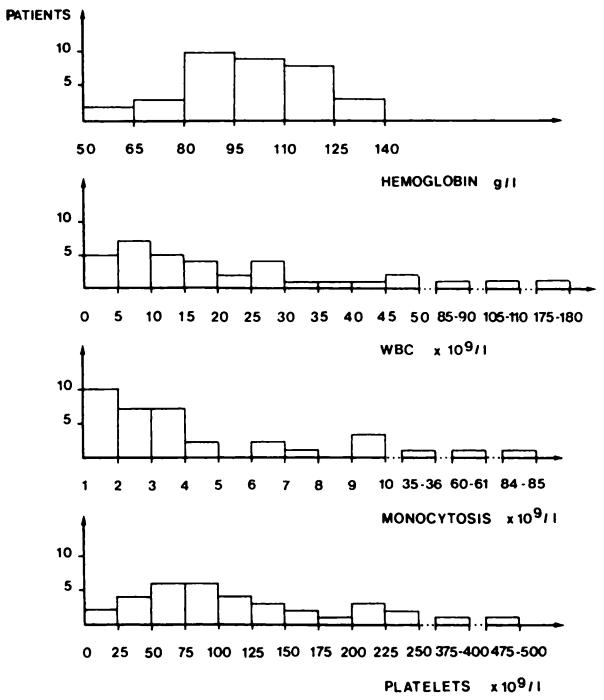

Fig. 1. Hematologic data of the 35 patients.

Bone marrow was hypercellular in all 35 patients. Mean bone marrow blast percentage was 11% (range 2%–28%). Myeloid elements were always increased in number, with a mean M/E ratio of 7/1. Absolute erythroblastopenia was present in 10 cases. An increase in bone marrow monocytic precursors was noted in 30 cases, with a mean percentage of 16% (range 2%–43%). Qualitative abnormalities of the BM erythroid cells include the presence of macroblasts (26 cases) or megaloblasts (4 cases), increased number of sideroblasts (7 cases)—in 2 cases, >15% ringed sideroblasts, and cytoplasmic abnormalities (basophilic stippling, clear unstained areas) in 7 cases. Myeloid cell abnormalities were best seen on bone marrow and peripheral blood PMN leukocytes: increased size (3 cases), hypersegmentation (13 cases) or hyposegmentation (Pelger-Hüet-like anomaly) (3 cases), and decreased number of primary granules (13 cases), some with a myeloperoxidase deficiency (3 cases). Dysmegakaryocytopoiesis was rarer and minimal. Ivy bleeding time was normal in all the 29 patients with blood platelet counts over 50 × 10^9/liter. No erythrocyte enzyme deficiency or hemoglobin electrophoresis abnormality was noted in the 25 cases tested. Bone marrow cell karyotype did not show a Ph[1] chromosome in any of the 25 cases studied. On bone marrow trephine biopsies, fibrosis was present in a diffuse and systematized reticulinic pattern in 12 cases (mild in 9 cases, severe in 3 cases), mutilating in 1 case, and in a localized pattern in 1 case.

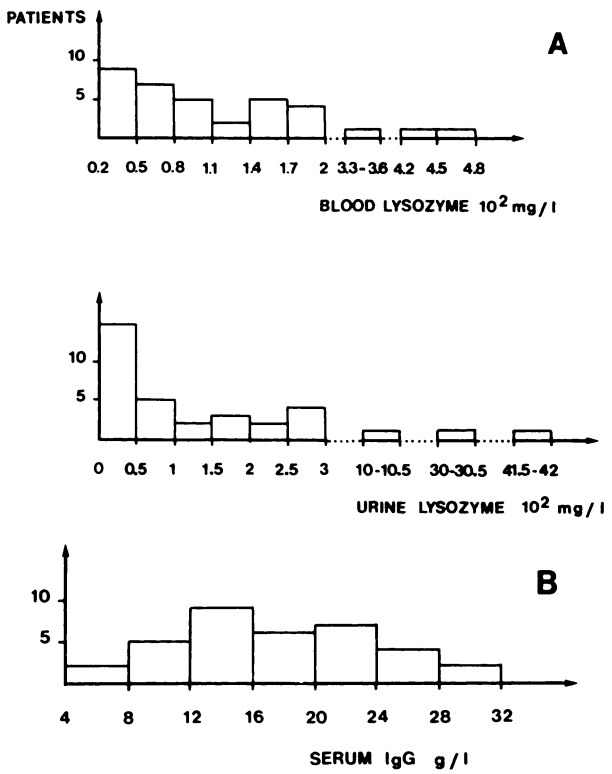

Fig. 2. Blood and urine lysozyme (A) and serum IgG (B) levels.

Biologic Findings

Blood and urine lysozyme levels before treatment are shown in Fig. 2A. Blood lysozyme level was increased in all 35 patients, with a mean of 107 ± 11.3 mg/liter (normal ≤15 mg/liter). Urine lysozyme levels were increased in 27 cases (77%), with a mean of 147 ± 123 mg/liter. Despite these high blood and urine lysozyme levels, renal failure and proteinuria were noted in only one patient who had the highest urine lysozyme level (4,200 mg/liter).

Immunologic Data

Prior to any treatment or RBC transfusion, an immunohematologic abnormality was noted in 14 of the 28 patients tested (50%). A positive Coombs' test for complement was noted in 5 cases (18%) and elution of an anti-I autoantibody was obtained in 13 cases, 9 of which had a negative Coombs' test. There was a significant increase in cold agglutinin titer in 4 cases.

Serum IgG levels are shown in Fig. 2B. Twenty-three patients (66%) had a polyclonal hypergammaglobulinemia (>14 g/liter), with mean levels as follows: IgG 19.9 ± 9 g/liter, IgA 5.54 ± 2.3 g/liter, IgM 3.28 ± 1.8 g/liter. A serum M component was observed in two cases, IgGλ in one, and IgGκ in one. None of these patients had multiple myeloma.

Relationship Between Quantitative Clinical and Biologic Parameters

The calculation of correlation coefficients showed some significant relationship among three groups of parameters: (1) WBC, monocytosis, and peripheral blast cells; (2) platelet counts, hemoglobin levels, and age; and (3) bone marrow blast cells and serum IgG. Principal component analysis confirmed that these three subsets of variables accurately summarized the data.

Treatment

In none of the 25 patients treated with hydroxyurea and/or 6-mercaptopurine was a complete remission (CR) obtained. In all these patients, there was an extreme sensitivity of leukocytosis to small doses of these antileukemic agents. In all 25 patients, a decrease in peripheral blood PMN leukocyte and monocyte counts was observed. In 12 patients, a decrease in splenic enlargement was noted during the treatment. No prolongation of survival related to this antileukemic therapy could be assessed.

Results of the treatment with low doses of cytosine-arabinoside are more promising. In one case, a CR (normal blood counts and bone marrow blast percentage) was obtained after one course of cytosine-arabinoside. During the 12 days that followed the treatment, an uncomplicated phase of pancytopenia was observed. In three cases, the CR was obtained after additional 15-day courses at 3–4-wk intervals (2 in 1 case, 3 in 2 cases). In two cases, death occurred before any result could be obtained: from liver cirrhosis in one case, and from sepsis in the other. Maintenance therapy of the CR was performed with 10-day courses of low-dose cytosine-arabinoside every 6–8 wk. Until July 1983, complete remission of 3 patients lasted 16+, 13+, 10+ mo. After a 10-mo CR, one patient rapidly developed a blast crisis under maintenance therapy.

Study of Survival

Survival was studied by Kaplan-Meier estimate without taking treatment into account. The median duration of survival for the 35 patients was 475 days (Fig. 3). The prognostic value of the following parameters has been tested and none had a prognostic significance: sex ($p = 0.52$), age ($p = 0.57$), spleen enlargement ($p = 0.71$), enlarged lymph nodes ($p = 0.64$), WBC ($p = 0.12$), blood monocytosis ($p = 0.59$), hemoglobin level ($p = 0.88$), platelet counts ($p = 0.36$), peripheral blood blast cells percentage ($p = 0.72$), bone marrow blasts percentage ($p = 0.83$), serum lysozyme levels ($p = 0.58$), urine lysozyme levels ($p = 0.84$), and serum IgG ($p = 0.96$). The

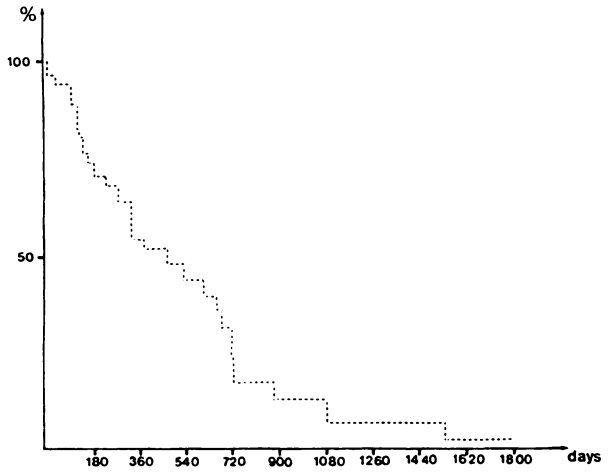

Fig. 3. Kaplan-Meier analysis of the survival of the 35 patients.

simultaneous Cox analysis of the parameters tested did not disclose any predictive information for survival.

Evolution toward an acute myeloid leukemia (more than 5% blast cells in the peripheral blood and/or more than 30% blast cells in the bone marrow) was observed in 7 patients 4, 5, 10, 11, 18, 51, and 72 mo after the diagnosis. All the patients with blast crisis died within 90 days. Fifteen patients died during the chronic phase from a cause directly related to cytopenia: infection in 10 cases and bleeding in 5 cases. Nine patients died during the chronic phase from an apparently unrelated disorder; in no patient was kidney failure the cause of death.

DISCUSSION

In 1970, Linman proposed the term "chronic myelomonocytic leukemia" for a myeloproliferative disorder characterized by a high peripheral monocytosis and a bone marrow proliferation of immature myeloid cells.[16] Thereafter, some authors suggested that a subacute variant could be distinguished, as some patients had a severe course, with death occurring within 12 mo of diagnosis from infection or hemorrhage.[7,17] Moreover, it rapidly became clear that CMML differed from other myeloproliferative syndromes by the presence of a severe dysmyelopoiesis, making this entity closer to the myelodysplastic syndromes (MDS). Therefore, some cases that could be considered as CMML were described in the category of refractory anemia with excess of blasts. All these discrepancies and/or changes in appellation created some confusion about this disorder. Reviewing cases of all types of myelodysplastic syndromes, the FAB cooperative group decided to include CMML into the larger group of MDS and to define diagnostic criteria. We described 35 patients fulfilling all these criteria. To our knowledge, they constitute the largest group described so far.

As in other myelodysplastic syndromes, CMML is a disease of the elderly without evidence of sex prevalence. Blood cell counts show moderate anemia with dyserythropoietic features, thrombocytopenia in 50% of the cases, and leukocytosis with monocytes and granulocytes in all stages of development. Bone marrow hypercellularity is a constant feature, involving mainly the granulocytic series. Monocyte infiltration is less prominent and absent in some cases. Dysplastic changes usually affect the erythroid, granulocytic, and megakaryocytic lineages, but it can be mild when neutrophil and monocyte counts are high.[9] A polyclonal increase in serum immunoglobulin levels was frequently observed, as previously noted in some reports.[8,18] This immune abnormality has not been reported in other myelodysplastic syndromes or in chronic myeloid leukemia (CML), suggesting that the monocytic proliferation is responsible for a polyclonal B lymphocyte activation. Normal monocytes exert both positive and negative regulatory controls on humoral immune responses.[19] Hyperimmunoglobulinemia in CMML could result from a nonspecific stimulation of B lymphocytes by clonal proliferation, or, as previously shown in other disorders,[20] the normal monocytic cells may not be able to exert their control over spontaneous immunoglobulin synthesis. Two of the 35 patients had a serum M component. Such an association has been previously described.[21] It could either be related to a B cell involvement in clonal proliferation, as in CML,[22] or to a random association of two geriatric disorders. An immunohematologic abnormality was present in 50% of the patients studied. As in other myeloproliferative diseases, its significance remains uncertain.[23] Blood lysozyme levels were increased in all patients and urine levels in 75%. Only one case of renal failure was observed. Despite lower blood and urine lysozyme levels, renal failure is more frequent in acute monoblastic leukemia.[24] These discrepancies suggest that additional mechanisms, such as leukemic infiltration of the kidneys, contribute to the renal failure of acute monoblastic leukemia. Clinical and biologic relation studies showed some links between parameters: the first one (WBC, monocytosis, peripheral blast cells) expresses the "leukemic component" of the disorder, and the second one (platelet counts, hemoglobin levels, age) expresses the "myelodysplastic component." The significance of the third one (bone marrow blast cell percentage, serum IgG levels) is unknown. Surprisingly, the blood lysozyme level was not related to any of these parameters.

Survival study shows that CMML has a poor prognosis. As in other myelodysplastic syndromes, death

often occurs during the chronic phase before blast crisis. Despite the large number tested, we could not find any parameter of prognostic significance. Our series is rather small but includes 28 deaths, and it has been previously shown that the power of a survival test is principally related to the number of deaths in the sample.[13] CMML is a disease of old age, but age has no prognostic significance, confirming that evolution depends only on the disease. These survival studies also show that CMML, as defined with FAB criteria, is a homogeneous disorder than can be individualized from other myeloproliferative and myelodysplastic syndromes. Especially, there is no parameter or group of parameters that could facilitate, at the time of diagnosis, the distinction of a subacute variant with a rapid evolution from a chronic one.

As yet, chemotherapy for CMML is disappointing. Aggressive therapy with drugs such as daunorubicin was responsible for deaths from pancytopenia.[8] 6-Mercaptopurine and/or hydroxyurea can decrease leukocyte counts, but requires a close survey of myelotoxicity and does not seem to significantly improve survival. Recently, Housset et al.[25] proposed small doses of ARA-C to treat chemoresistant AML. They suggested that ARA-C could have a differentiation action rather than an antimitotic effect.[25] We used this schedule of ARA-C chemotherapy as primary treatment of six cases of CMML. In four cases, a complete remission was obtained, always after a period of cytopenia. In one case, death from sepsis was related to neutropenia. Although preliminary, these results show that small doses of ARA-C over several consecutive days is a promising treatment for CMML. We could not confirm that ARA-C acts as differentiation agent, since pancytopenia and bone marrow hypoplasia occurred before complete remission was obtained. Further studies are needed to confirm the effectiveness of small doses of ARA-C in CMML and to determine if myelocytoxicity can be prevented by an adaptation of each course duration.

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REFERENCES

1. Quesenberry PJ, Levitt LJ: Hematopoietic stem cells. N Engl J Med 301:755, 1979

2. Gralnick HR, Galton DAG, Catovsky D, Sultan C, Bennett JM: Classification of acute leukemia. Ann Intern Med 87:740, 1977

3. Dreyfus B: Preleukemic states. Blood Cells 2:33, 1976

4. Broun GO: Chronic erythromonocytic leukemia. Am J Med 47:785, 1969

5. Bennett JM: Myelomonocytic leukemia. A historical review and perspectives. Cancer 27:1218, 1971

6. Sexauer J, Kass L, Schnitzer B: Subacute myelomonocytic leukemia. Clinical, morphological and ultra-structural studies of 10 cases. Am J Med 57:853, 1974

7. Zittoun R, Bernadou A, Bilski-Pasquier G, Bousser J: Les leucémies myélomonocytaires subaigues. Etude de 27 cas et revue de la littérature. Sem Hop Paris 48:1943, 1972

8. Zittoun R: Subacute and chronic myelomonocytic leukaemia: a distinct haematological entity. Br J Haemat 32:1, 1976

9. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C: Proposals for the classification of the myelodysplastic syndromes. Br J Haemat 51:189, 1982

10. Burkhardt R, Frisch B, Bartl R: Bone biopsy in haematological disorders. J Clin Pathol 35:189, 1982

11. Hansen NE: Lysozyme activity in leukemia. Semin Hematol 7:70, 1974

12. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457, 1958

13. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, Mc Pherson K, Peto J, Smith PG: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 35:1, 1977

14. Cox DR: Regression models and life tables. J R Stat Soc 34:187, 1972

15. Hotelling H: Analysis of a complex of statistical variables into principal components. J Educ Psychiatry 24:417, 1933

16. Linman JW: Myelomonocytic leukemia and its preleukemic phase (editorial). J Chron Dis 22:713, 1970

17. Zittoun R, Cadiou M, Kouzan S: Les éléments du pronostic des leucémies myelomonocytaires subaigues et chroniques. Ann Med Int 133:80, 1982

18. Miescher PA, Farquet JJ: Chronic myelomonocytic leukemia in adults. Semin Hematol 11:129, 1974

19. Rice L, Laughter AH, Twomey JJ: Three suppressor systems in human blood that modulate lymphoproliferation. J Immunol 122:991, 1979

20. Laughter AH, Lidsky MD, Twomey JJ: Suppression of immunoglobulin synthesis by monocytes in health and in patients with systemic lupus erythematosus. Clin Immunol Immunopathol 14:435, 1979

21. Barnard DL, Burns GF, Gordon J, Cawley JC, Barker CR, Hayhoe FGJ, Smith JL: Chronic myelomonocytic leukemia with paraproteinemia but no detectable plasmacytosis. Cancer 44:927, 1979

22. Fialkow PJ, Denman AM, Jacobson RJ, Lowenthal MN: Chronic myelocytic leukemia. Origin of some lymphocytes from leukemic stem cells. J Clin Invest 62:815, 1978

23. Rondeau E, Solal-Celigny P, Dhermy D, Vroclans M, Brousse N, Bernard JF, Boivin P: Immune disorders in agnogenic myeloid metaplasia. Relations to myelofibrosis. Br J Haematol 53:467, 1983

24. Tobelem G, Jacquillat C, Chastang C, Auclerc RF, Lechevallier T, Weil M, Daniel RT, Flandrin G, Harousseau JL, Schaison G, Boiron M, Bernard J: Acute monoblastic leukemia. A clinical and biologic study of 74 cases. Blood 55:71, 1980

25. Housset M, Daniel MT, Degos L: Small doses of ARA-C in the treatment of acute myeloid leukemia: Differentiation of myeloid leukemia cells? Br J Haematol 51:125, 1982

1984 63: 634-638

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