Acute Monoblastic Leukemia:
A Clinical and Biologic Study of 74 Cases

By Gérard Tobelem, Claude Jacquillat, Claude Chastang, Marie-Francoise Auclerc, Thierry Lechevalier, Marise Weil, Marie-Thérèse Daniel, Georges Flandrin, Jean-Luc Harrousseau, Gérard Schaison, Michel Boiron, and Jean Bernard

Seventy-four cases of pure acute monoblastic leukemia (AMoI) have been retrospectively studied. All patients were treated at Hospital Saint-Louis between 1970 and 1978. Diagnosis was based on morphological and cytochemical features according to the FAB classification. This type of leukemia occurred at any age and in both sexes, with a high frequency of extramedullary involvements. Hyperleukocytosis was very frequent and was significantly correlated with increased blood and urine levels of lysozyme, with renal failure and hypokalemia, and with coagulation abnormalities. AMoI still has a poor prognosis, despite a best remission rate (75%) obtained with rubidazone, since the duration of complete remission was short. Central nervous irradiation prolonged remission and prevented meningeal relapses, while 6 meningeal relapses occurred in the patients not irradiated. The high frequency of the extramedullary relapses, including gum and skin, emphasized the question of persistant blast cell sanctuaries after achievement of bone marrow remissions. A more intensive induction with several drugs active against monoblasts could be more efficient and prolong the duration of complete remissions.

MATERIALS AND METHODS

Seventy-four cases of AMoI have been studied. All were patients admitted to Hospital Saint-Louis between 1970 and 1978 and previously untreated. The diagnosis was based on examination of blood and bone marrow films according to the description of pure acute monocyctic leukemia of the Fab classification, split into poorly differentiated (type M5, I) and well differentiated (type M5, II) groups, and confirmed by cytochemical methods: peroxidase- and monocyte-specific Naphotol AS-D acetate esterase activity as previously described.145

Before treatment started, blood and urine lysozyme, serum potassium, blood urea nitrogen, and creatinine were measured routinely. Hemostasis was investigated before treatment by means of the prothrombin time, activated partial thromboplastin time, and determination of factor V, fibrinogen, and fibrinogen degradation products.

Seventy patients were treated: prednisone, 6-mercaptopurine and hydroxyurea in 3 cases; anthracyclines in 67 cases; daunorubicin in 18 cases; and rubidazone in 49 cases, as detailed in Table I. After 1976, when hematologic remission was obtained, central nervous system (CNS) prophylaxis was performed in 27 patients. In the 49 patients treated with rubidazone, monthly reinductions of AMoI protocol were as described in Table I. Statistical methods and significance levels are based on the log-rank test.57

RESULTS

Clinical Findings

Age and sex distribution are represented in Figure 1. The two sexes were involved with the same frequency: 39 females and 35 males. Two peaks were observed, one under 10 yr and the second after 40 yr of age. Of the 25 children under 10 yr, 16 were less than 1 yr old.

Clinical symptoms at the time of diagnosis are shown in Table I. The presence of tumor masses was striking, and extramedullary infiltration was frequent, especially of the skin and gums. The frequency of these different localizations was the same for both sexes and all ages.

Hematologic Findings

Initial blood values are presented in Figure 2. White blood cell count was, in most cases, over 10,000/cu mm, the median value for all the patients being 60,000/cu mm. Blast cells were usually, but not invariably, present in the peripheral blood. Hemoglobin level and platelet count were variable.

In 67 patients, subclassification (M5, I and M5, II) could be used, 58 patients were M5, I, and 9 were M5, II.

Biologic Findings

Blood and urine lysozyme. Blood lysozyme was evaluated before treatment in 39 patients and urine lysozyme in 32 patients. Blood lysozyme was increased...
Table 1. Therapeutic Regimens

**Induction**

- Daunorubicin 2 mg/kg/day
- Rubidazone 4 mg/kg/day
- Methotrexate 15 mg/sqm

**CNS Prophylaxis**
- irradiation
- 6 intrathecal injections (*)

**Monthly Reinduction**

- Cytosine Arabinoside 100 mg/sqm 12 hourly
- CCNU 100 mg/sqm one day
- Thioquanine 100 mg/sqm 12 hourly

For induction, 18 patients were treated by daunorubicin (*), 49 patients by rubidazone (0). After complete remission (CR), central nervous system (CNS) prophylaxis were performed in 27 patients. Monthly reinductions were given to the 49 patients treated by rubidazone.

In 32 patients (85%) and over 100 μg/ml in 20 patients (normal values under 10 μg/ml). Urine lysozyme was increased in 19 patients (60%) and over 30 μg/ml in 18 cases (normal values under 5 μg/ml). Increase of blood and urine lysozyme was significantly correlated with hyperleukocytosis ($p < 0.0001$ for blood lysozyme and $p < 0.05$ for urine lysozyme).

**Renal failure.** The findings of blood urea nitrogen over 0.70 g/liter and blood creatinine over 15 mg/liter before treatment has been considered as indicative of renal failure. Blood urea nitrogen and creatinine was measured before treatment in 69 patients, of whom 28 (40.5%) had renal failure by these criteria. The presence of renal failure was significantly correlated with hyperleukocytosis ($p < 0.05$). Renal failure and increased blood or urine lysozyme were also significantly correlated ($p < 0.05$ for blood lysozyme and $p < 0.03$ for urine lysozyme).

**Kalemia.** Sixty-nine patients had serum potas-

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*For the 35 males.
Fig. 2. Initial blood values. White blood cells (WBC) are expressed in $10^3$/cu mm; blood blast cells (Bl) in percentage of the WBC count; hemoglobin level (Hb) in g/100 ml; platelets (plat.) in $10^3$/cu mm.

Fig. 3. Actuarial duration of survival for the 74 patients.

Table 1. Initial blood values. White blood cells (WBC) are expressed in $10^3$/cu mm; blood blast cells (Bl) in percentage of the WBC count; hemoglobin level (Hb) in g/100 ml; platelets (plat.) in $10^3$/cu mm.

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sium measured before treatment, 14 cases (20.2%) had hypokalemia under 3 meq/liter, 4 of them under 2 meq/liter. Hyperkalemia has never been observed. Hypokalemia was significantly correlated with hyperleukocytosis ($p < 0.01$), with increased blood lysozyme ($p < 0.02$), and with increased urine lysozyme ($p < 0.01$).

Hemostasis. Sixty-one patients had investigations of hemostasis before treatment: 16 patients had findings consistent with the occurrence of disseminated intravascular coagulation (DIC) (factor V under 50%, fibrinogen under 2 g/liter, and increase of fibrinogen degradation products over 40 µg/ml). The presence of DIC before treatment was significantly correlated with hyperleukocytosis ($p < 0.001$). Only 6 of the 16 patients with DIC had clinical bleeding, and 3 of them received heparin and platelet transfusion.

Induction Treatment and Study of Complete Remission

Of the 74 patients, 4 died just after admission, before receiving chemotherapy. These were all men over 50 yr old, 3 of them with white-cell counts above 140,000/cu mm. Thus, 70 patients received induction chemotherapy as described in Materials and Methods. Forty-six patients (66%) achieved complete remission, 13 patients (18%) failed, and 11 (16%) died in aplasia.

Of the 18 patients treated with daunorubicin, 9 (50%) achieved complete remission, while 3 failed and 6 died during induction. Of the 49 patients treated with rubidazone, 37 (75%) had complete remission,
while 8 failed and 4 died during induction. None of the 3 patients treated without anthracyclines achieved a remission, and they all died during induction.

The median duration of complete remission (CR) in the 46 patients was 195 days. Figure 3 shows the actuarial duration of CR for 3 groups of treated patients: the median CR for 9 patients treated by daunorubicin was 65 days; the median CR for the 10 patients treated with rubidazole was 167 days; and for the 27 patients treated by rubidazole who received central nervous system prophylaxis, it was 254 days. The differences in median CR for the 3 groups were not statistically significant.

The median duration of CR was not significantly influenced by the following parameters: age, sex, tumoral syndrome, hyperleukocytosis, blood blast cell count, FAB subclassification (M5, L; M5, II).

Study of Relapses

When this retrospective study was closed in 1978, 31 of the 46 patients who achieved complete remission had relapsed, 3 had died in complete remission (unknown cause), and 12 were still alive in complete remission. Among the 31 initial relapses, 17 involved the bone marrow, 6 the CNS, and 5 the skin. Three patients had a first relapse involving bone marrow and skin; one of these three patients also had testicular infiltration and had meningeal leukemia. This last patient had had meningeal involvement at the time of initial diagnosis. None of the six patients who have a meningeal relapse were among the 27 patients who received central nervous system irradiation.

After a first extramedullary relapse (meningeal or skin), bone marrow relapse invariably occurred some weeks later, despite reinforcement of chemotherapy.

Study of Survival

The median duration of survival for the 74 patients was 158 days (Fig. 4). For the 67 patients treated by anthracycline it was 200 days; for the patients treated by daunorubicin, 125 days; and 270 days for the 49 patients treated by rubidazole. Figure 5 shows the actuarial duration of survival for the 46 patients who achieved complete remission: for the 9 patients treated by daunorubicin, the median duration of survival after remission was 210 days; for the 10 patients treated by rubidazole, it was 340 days; and for the 27 patients treated by rubidazole who received a central nervous system prophylaxis, it was 370 days. These differences were not statistically significant.

DISCUSSION

Diagnosis of AMol remains largely based on morphological and cytochemical features. But clinical and biologic characteristics are also consistent with this diagnosis. This study of 74 patients shows that this type of leukemia may occur at any age, without male or female predominance, but in this series, 2 peaks were observed, 1 of them in childhood and the other
AMoL appears to be a tumoral form of leukemia with a high frequency of skin and gum infiltration, as described before. These extramedullary involvements are probably due to the specific properties of monoblasts, as suggested by Litchmann and Weed. Hyperleukocytosis was very frequent: the median white cell count for our patients was of 60,000/cu mm. Acute respiratory obstruction has already been described in a case of AMoL with a very high white cell count and may have been responsible for leukostasis in 3 of 4 patients who died before treatment. Markedly elevated serum and urine lysozyme levels have been reported in AMoL, and our results confirmed these findings; furthermore, the increased lysozyme activities were significantly correlated with hyperleukocytosis and probably reflected the total leukemic cell mass. The high lysozyme levels before chemotherapy could be related to a spontaneous lysis of blast cells in vivo or to a release from intact leukemic cells. The follow-up of lysozyme levels during remission as a possible early indicator of relapse in now under investigation. Renal tubular dysfunction and hypokalemia have been reported with lyosymuria, and in this article we showed that they were significantly correlated with increased blood and urine lysozyme. Disseminated intravascular coagulation has been reported in some patients with AMoL, and in 26% of our patients, coagulation findings indicative of disseminated intravascular coagulation were observed before the start of treatment; clinical bleeding, however, was less severe than is usually seen in acute promyelocytic leukemia. The cause of disseminated intravascular coagulation could be a spontaneous release of thromboplastic material from monoblastic cells, but this remains to be proved.

The poor prognosis of AMoL rests mainly on small series or anecdotal reports, in which the rate of complete remission was less than 50%. In these reports, various drug regimens were used, including vincristine, cyclophosphamide, methylglyoxal, prednisone, and daunorubicin in some cases. The use of daunorubicin alone has produced some progress in induction, since 50% complete remissions have been obtained in our 18 patients treated by this drug. In combination with cytosine arabinoside, daunorubicin has been effective in 47% in a series of 17 treated patients. In a series of 10 children who received more than one dose of vinblastine, 60% achieved a complete or good partial remission, indicating that vinca alkaloids have a definite effect on the blast cells of AMoL. VP 16-213 seems to be an interesting drug, since of 8 reported cases, 5 entered complete remission. By the use of rubidazone, a high rate of complete remissions has been obtained in 49 cases of AMoL. The reasons for this might be: (1) a specific antimonoblastic activity of this drug, which is still difficult to assess; (2) an easier management with rubidazone, since the necessary dose may be attained progressively, one or two additional doses being effective during the regeneration phase without leading to resistance; (3) better supportive therapy of metabolic and hemorrhagic complications. Whatever the reason, 75% of our treated patients entered complete remissions. The complete remission rate did not appear to be influenced by age, sex, organ infiltration, or hyperleukocytosis, but the number of patients may have been too small for such an analysis.

Despite this encouraging remission rate, the duration of complete remission was still short despite monthly reinduction: 195 days for 46 patients who achieved complete remission. For the 10 patients of McKenna et al., it was 5 mo. In our series, central nervous system irradiation prolonged remission in the group treated by rubidazone, but the difference was not statistically significant, since the number of patients was too small and the duration still too short. But while 6 meningeal relapses occurred in the patients not irradiated, none were observed in those who received central nervous system prophylaxis. Irradiation thus seems to be an advance in the treatment of AMoL.

While bone marrow remission seemed to be relatively easy to achieve, especially in the group treated by rubidazone, the short duration of remission emphasizes the importance of the complete remission. In some cases, for instance, bone marrow remission was obtained while skin or gum infiltration had not completely disappeared. So it may be assumed that persistent blast cell sanctuaries, such as skin and/or gums, were not much affected by initial induction chemotherapy and were responsible for subsequent relapses. The study of the first relapse site was also very instructive, since extramedullary sites were involved in several cases. The question thus arises whether a more intensive induction with several drugs active against monoblasts, such as rubidazone, cytosine arabinoside, and VM 26 or vincristine in combination, might be more efficient and prolong the duration of the complete remission. Such a protocol has now been activated with a systematic cerebral nervous system prophylaxis.

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