

Acute megakaryoblastic leukemia: experience of GIMEMA trials

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The objective of the study was to evaluate the incidence, characteristics, treatment and outcome of acute megakaryoblastic leukemia (AMeL) in patients enrolled in GIMEMA trials. Between 1982 and 1999, 3603 new consecutive cases of AML aged over 15 years were admitted to GIMEMA trials. Of them, 24 were AMeL. The incidence of AMeL among AML patients enrolled in GIMEMA trials was 0.6% (24/3603). Diagnosis was based on morphological criteria. Out of 11 cytogenetic studies performed two presented chromosome 3 abnormalities. Twelve patients (50%) reached a CR, five (21%) died in induction and seven (27%) were unresponsive. The median duration of CR was 35 weeks (range 10–441). Seven patients underwent transplantation procedures (1 BMT, 4 aBMT, 2 aPBSCT). Four patients died in CR due to chemotherapy-related complications. Comparing the CR rate between AMeL and the other cases of AML enrolled in GIMEMA trials, no differences were observed. These results were mirrored for different age groups. The median survival was 40 weeks. At present, after a follow-up of a minimum of 2 years, only two patients are alive in CR, all the others having died. A 5-year Kaplan–Meier curve shows a disease-free survival of 17% and an actuarial overall survival of 10%. AMeL is a rare form of AML. The CR duration and the overall survival in this group of patients are very poor, even if similar to those observed in other AML. Furthermore, a high number of deaths in CR were observed. On the basis of these data, a specific therapeutic approach, possibly with innovative treatments, should be evaluated.

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Introduction

Acute megakaryocytic leukemia (AMeL) is a rare form of acute myeloid leukemia (AML). Even if it is a well-known entity, it could be frequently misdiagnosed as acute myelosclerosis. From 1931, when it was firstly described,¹ reports have been sporadic because of both the rarity of the disease and the lack of well-established diagnostic criteria. AMeL occurs in all age groups with two peaks in distribution: one in adults and the other in children.² In particular, children with Down syndrome appear to have an increased incidence of AMeL.^{3,4} Furthermore, AMeL seems frequently associated with some other malignancies such as primary mediastinal germ cell tumors.^{5–7}

The incidence of this form of AML shows a high variability according to the different reports. Some authors suggest that it ranges from 8 to 15% of all acute leukemias, while a recent study by Tallman *et al*⁸ for ECOG reported an incidence of 1.2% (20 patients) among a population of 1649 patients

enrolled in ECOG trials during a 15-year period. Although a good percentage of patients achieve complete remission (CR), only a few patients survive beyond 5 years.^{9–12} Clinical experience with this rare leukemia remains limited.

In our study we analyzed the laboratory and clinical features, biological characteristics and outcome of patients with AMeL treated according to Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) protocols during a 17-year period.

Materials and methods

Patients

The study population comprised 3603 patients, aged 15–76 years, with newly diagnosed acute myeloid leukemia (AML), entered on 10 trials for previously untreated AML conducted during the period February 1982–July 1999 by the GIMEMA and observed in 62 Hematology Divisions in tertiary care or University Hospitals.

The medical records of 24 patients with AMeL were retrospectively reviewed.

The following parameters were evaluated: demographic data (age, gender), morphological, immunophenotypic, cytogenetic studies performed at onset of AMeL, white blood cells (WBC), hemoglobin (Hgb) and platelet count at diagnosis of AMeL, clinical presentation, induction treatment, complete remission (CR) achievement and duration, overall survival from AML diagnosis. Furthermore, these parameters were compared with those of the other patients with AML, except acute promyelocytic leukemia, enrolled in the same therapeutic trials.

The diagnosis of AMeL was first established at each institution, and subsequently centrally reviewed at the time of the study entry. The bone marrow aspirate or biopsy leukemic blast cell population represented 30% or more of the myeloid marrow. The majority of these cells were undifferentiated and therefore almost all negative for myeloperoxidase staining by routine immunocytochemistry methods. Some were easily identified by early or dysplastic megakaryocytic precursors. These were the main diagnostic criteria according to the FAB classification.¹³ Confirmation of the cell of origin was performed by immunocytochemistry stain for factor VIII on the bone marrow biopsy, or the presence of antibodies against glycoprotein IIb/IIIa (CD41a) or glycoprotein IIIa (CD61). Myelofibrosis as demonstrated with a reticulin stain was strongly positive in most cases.

Immunophenotyping for platelet-specific glycoproteins (GP) were used to characterize acute leukemia cells: CD41

(GPIIb/IIIa), or CD42 (GPIb), CD36 (GPIIb), CD61 (GP IIIa). Membrane and cytoplasmic markers were considered positive when present on more than 20% of the blast cells.

Treatment

Patients with AMeL were identified from the GIMEMA database of patients entered on the following clinical trials for previously untreated AML: LANL 8201, LANL 8202, LANL 0388, EORTC-GIMEMA AML 8A and 8B, LANL 0491 (unpublished data), LANL 93 and AML10p (pilot studies for EORTC-GIMEMA AML 10) EORTC-GIMEMA AML 10, and LAM 0594. Data on treatment schedule of each trial have already been reported.^{14–20}

Statistical analysis

The major clinical characteristics of patients studied were compared to those of the whole AML population recorded in the GIMEMA. Non-parametric Mann–Whitney test was used to analyze statistical difference on distribution of continuous variables. Stratified analysis and adjusted ORs were computed by Mantel–Haenszel method. χ^2 test of Fisher's exact test was used for differences on frequencies. Survival curves were developed according to the Kaplan–Meier method and were compared with the use of log-rank test.

Results

Clinical and laboratory characteristics at presentation

Between 1982 and 1999, 3603 patients were considered eligible for chemotherapy. Twenty-four patients had AMeL (0.6%). None of these patients had a secondary AMeL. No significant differences were found in the distribution of AMeL cases during the time, except for the first period (1982–1984: 0/409 0%; 1985–1987: 2/261 0.76%; 1988–1990: 5/701 0.71%; 1991–1993: 5/671 0.74%; 1994–1996: 7/1137 0.61%; 1997–1999: 5/424 1.1%). Fourteen of the 24 patients (58%) were men and 10 (42%) were women. The median age was 51 years ranging from 15 to 76 years. The median white blood cell (WBC) count was $7.1 \times 10^9/l$ (range 0.5–162), the median hemoglobin level was 8 g/dl (range 3.6–13), and the median platelet count was $66 \times 10^9/l$ (range 20–572). The median peripheral blast percentage was 19% (range 0–80%) and the median percentage of blasts in the bone marrow was 74.5% (range 30–99%) (Table 1). Marrow fibrosis was present in the

Table 1 Clinical and laboratory features of the study group at the time of diagnosis

| | Total (n = 24) |
|---|-----------------|
| Median age (range) | 51 (15–76) |
| Sex (M/F) | 14/10 |
| Fever | 8 (27%) |
| Lymphadenopathy | 1 (3%) |
| Hepatomegaly | 11 (37%) |
| Splenomegaly | 9 (30%) |
| Hemoglobin (g/dl) (median, range) | 8 (3.6–13) |
| WBC ($\times 10^9/l$) (median, range) | 7.1 (0.5–162.0) |
| Circulating blasts (%) (median, range) | 19 (0–80) |
| Bone marrow blast cells (%) (median, range) | 74.5 (30–99) |
| Platelets ($\times 10^9/l$) (median, range) | 66.0 (20–572) |

bone marrow core biopsy specimens of all the patients in whom it could be assessed (13 patients), and in particular, eight patients (33%) had extensive fibrosis.

Extramedullary involvement was present on clinical ground at the time of diagnosis in the skin in two patients. None of the patients had Down syndrome.

Cytogenetic studies

Eleven of the 24 patients had cytogenetic studies carried out. Karyotype analysis was normal in two cases. Two patients had a chromosome 3 abnormality (one patient 46, XX inv3 (q21;q26) and another patient 46, XX t (3;17)(p13;p11) translocation). Two other cases had different chromosomally abnormal clones (46, XX, 14p+ and 46, xy/45, XY, -7). Five patients had no metaphases. Thirteen patients had no cytogenetic studies performed (Table 2).

Immunophenotype

Because of marrow fibrosis, immunophenotyping studies on bone marrow blasts were successful in only 15 patients. Myeloperoxidase was negative in the majority of the blast cells. HLA-DR and CD34 were commonly expressed and the leukemic cells were positive for one to two platelet-specific antigens in addition to the lack of myeloperoxidase or an antigen profile consistent with a lymphoid leukemia (Table 2).

Outcome

CR was achieved in 12 of the 24 patients (50%) (Table 3). Five patients died in induction (21%), and the remaining seven patients (29%) had resistant disease. The causes for deaths in induction were infection (four cases) and cerebral hemorrhage (1 patient). The median duration of aplasia (neutrophil count $<0.5 \times 10^9/l$) after induction therapy was 24 days (range 15–40), while the median duration of aplasia after consolidation was 20 days (range 15–36).

Remission duration and overall survival

The median remission duration among patients achieving CR was 35 weeks with a range of 10 to 441+ weeks. One patient died in CR from infection. Among the remaining 11 patients in CR, seven patients (64%) underwent bone marrow transplantation (BMT) (one allogeneic and six autologous (four autologous BMT, two autologous peripheral blood stem cells transplantation (aPBSCT)). Three patients died during transplantation (two aBMT and one aPBSCT): two patients from drug-related toxicity and one due to pulmonary aspergillosis. At present, after a minimum follow-up of 2 years only two patients are in CCR. Among the six relapsed patients, four had a bone marrow relapse and two had a contemporaneous bone marrow and central nervous system (CNS) relapse. The actuarial Kaplan–Meier survival curve shows a disease-free survival (DFS) of 17% at 5 years (Figure 1).

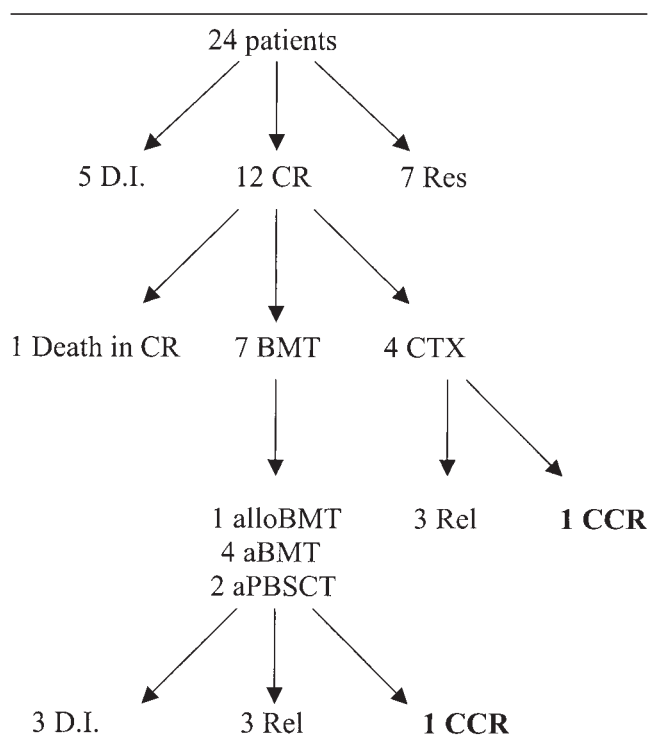
The median overall survival for all patients was 40 weeks; ranging from 2 to 444+ weeks. Eight patients survived more than 1 year; of these, five achieved CR. At present, two patients are still alive. Among the four patients who had a post-transplantation engraftment, only one is still alive. The

Table 2 Karyotype and immunophenotype and platelet antigen expression of patients with AMeL

| Patient | GIMEMA trial | Age | Gender | Karyotype | Immunophenotype/Immunohistochemical stain (positive) |
|---------|--------------|-----|--------|-----------------|--|
| 1 | 8201 | 39 | F | 46,XX,inv(3) | N/A |
| 2 | 0388 | 61 | M | N/A | N/A |
| 3 | 0388 | 65 | M | N/A | N/A |
| 4 | 0388 | 76 | F | N/A | N/A |
| 5 | LAM0591 | 65 | M | 46, XX | N/A |
| 6 | LAM0594 | 67 | M | N/A | N/A |
| 7 | AML8A | 24 | M | N/A | CD2, CD3, CD5, CD13, CD33, CD34, CD41 |
| 8 | AML8A | 26 | M | No metaphases | N/A |
| 9 | AML8A | 15 | M | N/A | CD42 |
| 10 | AML8A | 32 | M | No metaphases | N/A |
| 11 | AML8A | 51 | F | 46XX,14p+ | N/A |
| 12 | AML8B | 52 | F | No metaphases | CD13, CD33, CD34, CD61, CD170, HLA-DR |
| 13 | AML10 | 44 | M | 46xy/45xy,-7 | CD41, CD34, HLA-DR |
| 14 | AML10 | 33 | F | N/A | CD41, CD13, CD34 |
| 15 | AML10 | 51 | M | N/A | CD34 |
| 16 | AML10 | 58 | F | No metaphases | CD41, CD13, CD61, CD34 |
| 17 | AML10 | 39 | F | t(3;17)(p13;11) | CD13, CD33, CD34, CD7, HLA-DR |
| 18 | AML10 | 45 | F | No metaphases | N/A |
| 19 | AML10 | 56 | M | N/A | CD33, CD38, CD62, HLA-DR |
| 20 | AML10 | 42 | M | N/A | CD13, CD33, CD25 |
| 21 | AML10 | 60 | M | N/A | CD13, CD33, CD34, HLA-DR, CD36 |
| 22 | AML10 | 57 | M | 46 XY | N/A |
| 23 | AML10 | 52 | F | N/A | CD13, CD33, CD34, CD41, CD42, CD61 |
| 24 | AML10 | 32 | F | N/A | CD33 |

N/A, not performed.

Table 3 Therapeutic options and outcome of 24 patients with AMeL



CR, complete remission; D.I., death in induction; Rel, relapse; Res, resistant; CTX, chemotherapy; CCR, continue CR; BMT, bone marrow transplantation; alloBMT, allogeneic; aBMT, autologous; aPBSC, autologous peripheral blood stem cell transplantation.

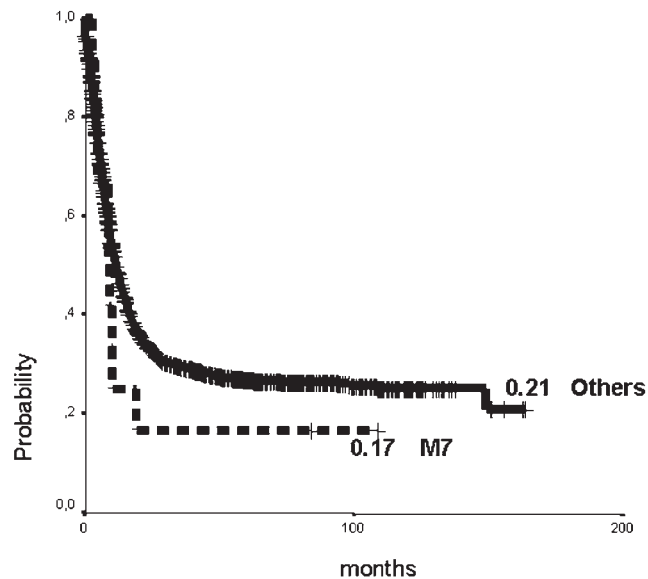


Figure 1 Disease-free survival (M7 vs Others).

other relapsed and died. The actuarial Kaplan–Meier survival curve shows an overall survival (OS) of 10% at 5 years (Figure 2).

Among the seven patients resistant to the induction treatment, only two patients were responsive to a second-line treatment (fludarabine, cytarabine and rhG-CSF (FLAG) and mitoxantrone, etoposide and cytarabine (MEC) respectively). All the others died due to leukemia progression.

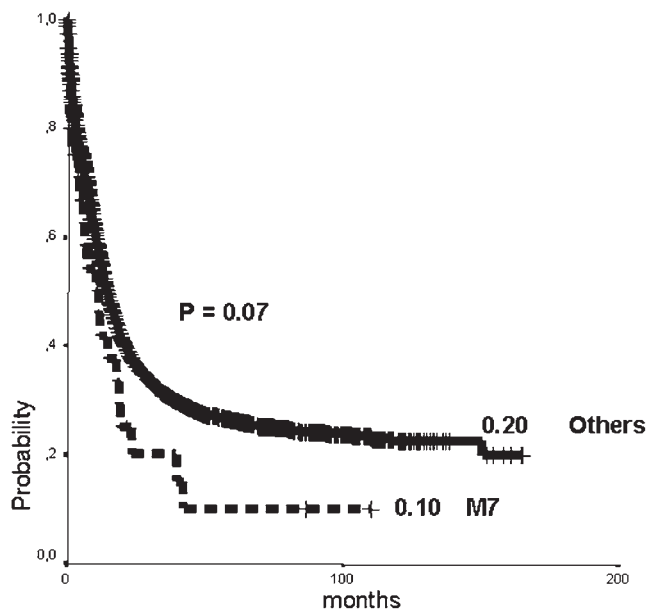


Figure 2 Overall survival (M7 vs Others).

Comparison between AMeL and AML enrolled in GIMEMA trials

Although a comparison of the clinical features of only 24 cases of AMeL with other subtypes of AML is difficult because of the small numbers of AMeL cases, some observations can be made. Comparing the CR rate between AMeL and all the other evaluable cases of AML observed in the same period of time, no difference was observed (12/24 (50%) vs 2098/3603 (58%), OR 0.72% CI 95% 0.30–1.71, $P = ns$). Similar results were observed stratifying the patients for age (<60 and >60) (<60: 11/20 vs 1795/2949, OR 0.79, 95% CI 0.30–2.06, $P = ns$) (>60: 2/4 vs 303/654, OR 1.16, 95% CI 0.12–11.54, $P = ns$). No differences were observed comparing the DFS (Figure 1) and the OS between the two groups. Only a non-significant unfavourable trend for AMeL ($P = 0.07$) was observed for the OS (Figure 2).

Discussion

Before 1985, when the FAB group defined precise morphologic criteria for diagnosis,¹³ AMeL was not a well codified entity. In the following years when immunophenotyping by flow cytometry became a widely employed method to improve diagnosis, the association of immunocytochemistry and/or immunophenotype allowed a correct diagnosis. In fact, cells from patients with AMeL express the typical megakaryocyte-platelet lineage-specific markers.^{20–22}

In this study we report the experience of GIMEMA during a 17 year period. We collected 24 patients with AMeL cases with diagnosis confirmed at central review. Our data on epidemiology of AMeL are similar to those reported by the ECOG group. In fact, the incidence of AMeL that we found was 0.6%, similar to that observed by Tallman *et al*, (1.2%, among AML adult patients). However, in our experience the incidence was found to be lower in respect to previously reported series in pediatric patients (8–14%).^{8–12,23} This discrepancy could be due in part to the fact that in pediatric series patients with Down syndrome are observed and, among these, AMeL

occurs about 400–500 times more frequently than in other children.²⁴ In fact, among the 24 AMeL cases identified by Ribeiro *et al*,¹⁰ there were five Down syndrome patients (20%), and in the series by Athale *et al*,¹² Down syndrome patients represented 14.6% of all AMeL cases. Another possible explanation could be that AMeL occurs more frequently in children than in adults. One additional explanation for the discrepancy in the incidence of AMeL reported here and in earlier series could be improvement in the more precise diagnostic criteria now available, and that in the past, other hematological disorders associated with fibrosis in the marrow such as myelofibrosis and acute myeloid leukemia may have been included in these series.

The St Jude Children's Research Hospital group, in their recent revision of cases of AMeL, reported that among 41 cases a consistent proportion was represented by secondary AMeL (six cases, 14.6%) occurring after treatment for Blineage acute lymphoblastic leukemia.¹² In contrast, none of the cases enrolled in GIMEMA trials had a secondary AMeL.

The absence of AMeL cases in our series between 1982 and 1984 is obviously justified by the fact that FAB criteria for identification of AMeL were suggested only in 1985; however, in the following years, the observation of AMeL cases has remained steadily low.

The prognosis of this category of patients is generally bad. In spite of a good percentage of CR achievement, that could range, according to the different studies on pediatric and adults series, between 50% and 78%, the DFS is very short, with a median of 10 months.^{8–12} In our study, these results were confirmed. We observed a CR rate of 50% with a median DFS of 9 months. Despite the lack of statistical difference for DFS and OS comparing AMeL and other AML enrolled in GIMEMA trials, a trend for a worst prognosis was observed for AMeL patients.

It is noteworthy that a high percentage of patients presented extramedullary localizations. In fact, two patients showed a skin infiltration at diagnosis, and two a CNS involvement at relapse. These data suggest that AMeL, as well as M4 and M5 FAB subtypes, could have an extramedullary involvement, as also observed in some other reported cases.^{25–26}

The majority of our patients who achieved a CR underwent transplantation procedures (7/12, 58%). Data regarding BMT in AMeL are very scanty, and a few reports suggest that allogeneic BMT can have good long-term results.²⁷ Our results on transplantation procedures are not encouraging. In fact, six out of seven transplanted patients died within a few months of the procedure, three from toxicity during the engraftment phase, while three others had an early relapse. It is possible that in AMeL patients, transplantation procedures could cause a more relevant damage of the marrow stromal microenvironment, as already reported in patients undergoing BMT.²⁸ This hypothesis could find support in the data concerning post-chemotherapy aplasia, which is seen to last longer than expected.

Considering that we also observed one patient who died from toxicity during the consolidation phase, we observed a high percentage of death in CR (33%), more relevant in respect to that reported in other clinical trials for AML. These results suggest that although improvement in the CR rate is needed, improved post-remission therapy is advisable.

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