CLINICAL SCIENCE

# Improving the outcomes of elderly patients with acute myeloid leukemia in a Brazilian University Hospital

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**OBJECTIVE:** To evaluate the outcomes of acute myeloid leukemia patients who were older than 60 years of age at the time of diagnosis following the implementation of a treatment algorithm based on age, performance status, and cytogenetic results.

**METHODS:** We retrospectively compared the results of 31 elderly acute myeloid leukemia patients (median age of 74 years) who were treated according to the new algorithm.

**RESULTS:** Fifteen patients with a good performance status and no unfavorable karyotypes were treated with either intensive cytotoxic chemotherapy (<70 years, nine cases) or adapted etoposide, 6-thioguanine and idarubicine (>70 years, six cases); 16 cases with a poor performance status or unfavorable cytogenetics received supportive care only. Six patients achieved a complete remission and two achieved a partial remission after chemotherapy. There were three toxic deaths during induction, two in the adapted etoposide, 6-thioguanine and idarubicine group and one in the intensive cytotoxic chemotherapy group. The overall median survival time was 2.96 months, 1.3 months in the supportive care group, and 4.6 months in the treatment group.

**CONCLUSIONS:** Our results illustrate the importance of treatment guidelines adapted to local resources in an attempt to improve the survival of elderly acute myeloid leukemia patients in developing countries.

**KEYWORDS:** Acute Myeloid Leukemia; Elderly; Intensive Chemotherapy; Adapted ETI; Prognosis.

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## INTRODUCTION

Acute myeloid leukemia (AML) comprises a heterogeneous group of clonal myeloid precursor cell disorders with distinct clinical, morphologic, immunophenotypic, cytogenetic, and molecular features.

Age is one of the most important predictors of outcomes in adult AML, and 20-30% of patients are older than 60 years of age at the time of diagnosis.[1] The unfavorable prognosis of elderly patients may be related to their poor performance status, an increased incidence of high-risk cytogenetic abnormalities, the common expression of multidrug resistance phenotypes, and the presence of previous hematologic disorders.[2] The treatment of elderly AML patients is challenging, with poor response rates and high mortality rates following intensive chemotherapy.[3] A previous study from our group[4] had similar findings, reporting an adverse outcome in AML patients older than 60 with no impact of intensive treatment on overall survival time.

The last two decades have brought few advances in the outcomes and survival of elderly patients with AML despite the introduction of new therapy modalities, including granulocyte colony-stimulating factors, modulating drugs of the multidrug resistance status and FLT3 inhibitors. Although several centers recommend that the best treatment for this group of patients is inclusion in new clinical trials, some elderly patients may benefit from intensive chemotherapy regimens. The correct selection of treatment remains fundamental to the management of this disease.[1,2]

Consistent with the above evidence and to improve our results, we retrospectively evaluated the outcomes of elderly AML patients treated at the Escola Paulista de Medicina, Universidade Federal de São Paulo after the implementation of an adapted treatment algorithm based on age, performance status, and cytogenetic results that benefited from the

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participation of a multidisciplinary team and the continuous training of medical and nursing staff.

## MATERIALS AND METHODS

### Patients

The sample comprised 31 patients greater than 60 years of age with a de novo AML diagnosis or with a previous history of myelodysplastic syndrome. All the participants had been diagnosed at the Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP) between January 1, 2003 and July 31, 2008, and the sample represented 26.27% (31/118) of all the adult AML cases diagnosed in the institution during this period. The outcomes of all the patients were followed until death. The clinical features at presentation of all 31 patients are shown in Table 1. This study was conducted according to the requirements of the Institutional Review Board of UNIFESP.

### Cytomorphologic, immunophenotypic, and cytogenetic studies

Peripheral blood (PB) and bone marrow (BM) smears collected using BM first-pull aspiration were stained with May-Grünwald-Giemsa (MGG), and cell morphology was analyzed using conventional bright-field microscopy.

Immunophenotypic studies were performed in BM samples using a four-color combination of monoclonal antibodies (MAbs). Immunofluorescence staining was performed using a standardized direct stain-and-then-lyse-and-wash technique combined with fixation and permeabilization for the detection of intracellular antigens. Immediately after staining, samples were acquired using a FACSCalibur flow cytometer (Becton-Dickinson, San Jose, CA, USA) using the CellQuest software program (Becton-Dickinson, San Jose, CA, USA).

For cytogenetic analysis, 5 ml of each BM samples was collected in a syringe containing sodium heparin. Karyotyping was performed using standard techniques, and the results were reported according to the International System for Human Cytogenetic Nomenclature guidelines.[5] At least 20 G-banded metaphases were analyzed. A clone was defined either as two BM cells showing the same gain of chromosomal material or the same structural aberration or as at least three BM cells showing loss of the same chromosome. A complex aberrant karyotype was defined as three or more independent cytogenetic abnormalities in at least two BM cells. Cytogenetic risk was defined according to the National Comprehensive Cancer Network guidelines.[6]

AML was diagnosed and classified according to the World Health Organization (WHO) criteria, which define AML as the presence of at least 20% of blasts in a BM sample or the presence of a recurrent cytogenetic abnormality.[7]

### Treatment protocols

Patients were treated according to their age, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, and cytogenetic risks and were divided into two groups: treatment and supportive care.

In the treatment group, patients younger than 70 years of age with a good performance status (ECOG index <II) and no unfavorable karyotypes were treated with intensive cytotoxic induction chemotherapy comprising intravenous (IV) cytarabine (200 mg/m$^2$ per day for seven days) and IV daunorubicin (45 mg/m$^2$ per day on days 1-3). Patients who were older than 70 years of age but had a good performance status and no unfavorable cytogenetics were treated with an alternative chemotherapy regimen adapted from the Finnish Leukemia Group (ETI protocol),[8-10] which comprised IV

**Table 1 -** Patient characteristics at the time of diagnosis in the two groups.

| | Supportive care (n = 16) | Treatment (n = 15) | |
|---|---|---|---|
| | | Adapted ETI (n = 6) | Intensive treatment (n = 9) |
| **Median age (range)** | 79 (60-89) | 77 (68-80) | 68 (60-75) |
| **Gender (male/female)** | 6/10 | 3/3 | 6/3 |
| **ECOG performance status** | | | |
| 0 | 1 | 1 | 1 |
| I | 8 | 5 | 8 |
| II | 3 | 0 | 0 |
| III | 4 | 0 | 0 |
| IV | 0 | 0 | 0 |
| **Karyotype** | | | |
| Low risk | 0 | 2 | 1 |
| t(8;21) | *0* | *1* | *1* |
| inv(16) | *0* | *1* | *0* |
| Standard risk | 8 | 1 | 3 |
| Normal | *3* | *1* | *2* |
| del(20 q) | *0* | *0* | *1* |
| +8 | *3* | *0* | *0* |
| t(8;16) | *2* | *0* | *0* |
| Unfavorable risk | 4 | 1 | 1 |
| complex karyotype | *1* | *1* | *0* |
| del(7) | *1* | *0* | *1* |
| t(1;3) | *1* | *0* | *0* |
| del(11 q)(23) | *1* | *0* | *0* |
| Unknown | *4* | *2* | *4* |
| **Hb (g/dL)** | 8.53 | 6.5 | 6.5 |
| **WBC ($\times 10^9$/L)** | 56.5 | 21.6 | 20.1 |
| **Platelets ($\times 10^9$/L)** | 58 | 38.7 | 30 |
| **Bone marrow blast cells (%)** | 57.5 (21-97) | 56.5 (20-92) | 46 (20-79) |
| **Splenomegaly** | 3/16 | 1/6 | 1/9 |

etoposide (80 mg/m$^2$ twice daily on days 1-5); IV thioguanine (100 mg/m$^2$ twice daily on days 1-5) and IV mitoxantrone (12 mg/m$^2$ once daily on days 1-3). The original ETI protocol contained idarubicine, which was replaced by mitoxantrone in our study because of the unavailability of this chemotherapeutic agent in our hospital and the similar pharmacodynamic features of both drugs. The response assessment criteria were defined according to the guidelines reported by Cheson et al.[11]

Complete remission was defined by the following criteria: the presence of <5% blast cells; the absence of blasts with Auer rods; the absence of extramedullary disease; an absolute neutrophil count $>1.0\times10^9$/l and a platelet count $>100\times10^9$/l. Partial remission was defined as a decrease in BM blast percentage to 5-25% and a decrease in the pretreatment BM blast percentage by at least 50%. The overall survival time was the time measured from the date of leukemia diagnosis to the date of death from any cause. After the achievement of complete remission, consolidation therapy was identical to induction therapy in both treatment schedules. Granulocyte colony-stimulating factor was administrated to all patients who presented with a neutrophil count $<0.5\times10^9$ cells/l after chemotherapy administration.

Patients with a poor performance status and those with unfavorable cytogenetics were treated with supportive care, regardless of age. Monotherapy with hydroxycarbamide 500-1500 mg/day was initiated when the white blood cell count was $>20\times10^9$/l, and blood cell transfusions and antibiotic therapy were administrated when necessary.

### Statistical analyses

Analyses were performed on an intention-to-treat basis. The response rates of the different patient groups were compared using the chi-squared ($\chi^2$) test of proportions. Overall survival time was estimated with the Kaplan-Meier method and compared using the log-rank test. A $p$-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 12.0 software (Chicago, USA).

## RESULTS

### Patient characteristics

The median age was 74 years (range 60 to 89 years), and the male:female ratio was 1:1. Fifteen patients received treatment [nine with intensive chemotherapy and six with adapted etoposide, 6-thioguanine and idarubicine (ETI)], and 16 received supportive care. The median ages in the treatment and supportive care groups were 68 and 79 years old, respectively. According to the WHO classification criteria, the cases were subdivided into the following groups: three cases of AML with recurrent translocations (two with t(8;21) and one with inv(16)); 11 cases of AML with myelodysplasia-related changes; one case of therapy-related AML and 16 cases of AML not otherwise specified (one case of AML with minimal difference, four of AML without maturation, four of AML with maturation, two of acute myelomonocytic leukemia, three of acute monoblastic leukemia and two of erythroleukemia). At diagnosis, the patients' hemoglobin levels ranged from 2.9 to 15.5 g/dl (median 7.5 g/dl), and the white blood cell counts ranged from 1.1 to $128\times10^9$ cells/l (median $39.5\times10^9$ cells/l). The ECOG performance status, the BM blast cell percentage, and the presence of splenomegaly are listed in Table 1.

Cytogenetic studies were performed in 29 patients, and 21 (72.4%) presented the following karyotype results: three had low-risk abnormalities (14.3%), twelve had intermediate-risk abnormalities (57.1%) and six had high-risk abnormalities (28.6%).

### Response and survival time

Table 2 shows the overall responses of the AML patients by patient group. In the intention-to-treat analysis used, the overall response (complete remission + partial remission) of the patients who received treatment (8 of 15 patients, 53.3%) was superior to the response of the patients in the supportive care group (0 of 16 patients) ($p<0.05$). Of the six patients who achieved complete remission following induction, five received intensive therapy, and one received adapted ETI. In all, two patients achieved a partial response, and both were in the ETI group. One patient presented with treatment failure after ETI, and three patients presented with treatment failure after intensive chemotherapy. Three toxic deaths occurred during induction: two in the adapted ETI group and one in the intensive chemotherapy group. All the toxic deaths were due to severe infection.

The overall median survival time was 2.96 months (range 0.07 to 9.5): 1.3 months in the supportive care group and 4.6 months in the treatment group. The $p$-value produced by the log-rank test was $p=0.001$ for the comparison between the two groups. The treatment comparisons in terms of overall survival time are shown in Figure 1.

Patients older than 70 years of age exhibited a median survival time of 2.8 months, and no significant difference was observed between them and the patients less than 70 years old (3.4 months, $p=0.86$).

### Time of hospitalization

The median duration of hospitalization was 1.6 months overall (range 0.07 to 5.2) and 0.56 and 2.8 months in the supportive care and treatment groups, respectively. The rate of hospitalization during the follow-up period did not vary significantly by patient group (75.7% for the supportive care group and 77.6% for the treatment group).

**Table 2 -** Response rates and overall survival times by patient group.

| | Supportive care (n = 16) | Adapted ETI (n = 6) | Intensive treatment (n = 9) | ETI + intensive treatment (n = 15) |
|---|---|---|---|---|
| **Response rate** | | | | |
| Complete remission | 0 | 1 | 5 | 6 |
| Partial remission | 0 | 2 | 0 | 2 |
| Resistant disease | 16 | 1 | 3 | 4 |
| Death during induction | 0 | 2 | 1 | 3 |
| **Overall survival time in months (range)** | 1.3 (0.07-9.2) | 4.4 (1.05-7.25) | 4.6 (0.92-9.5) | 4.6 (0.92-9.5) |

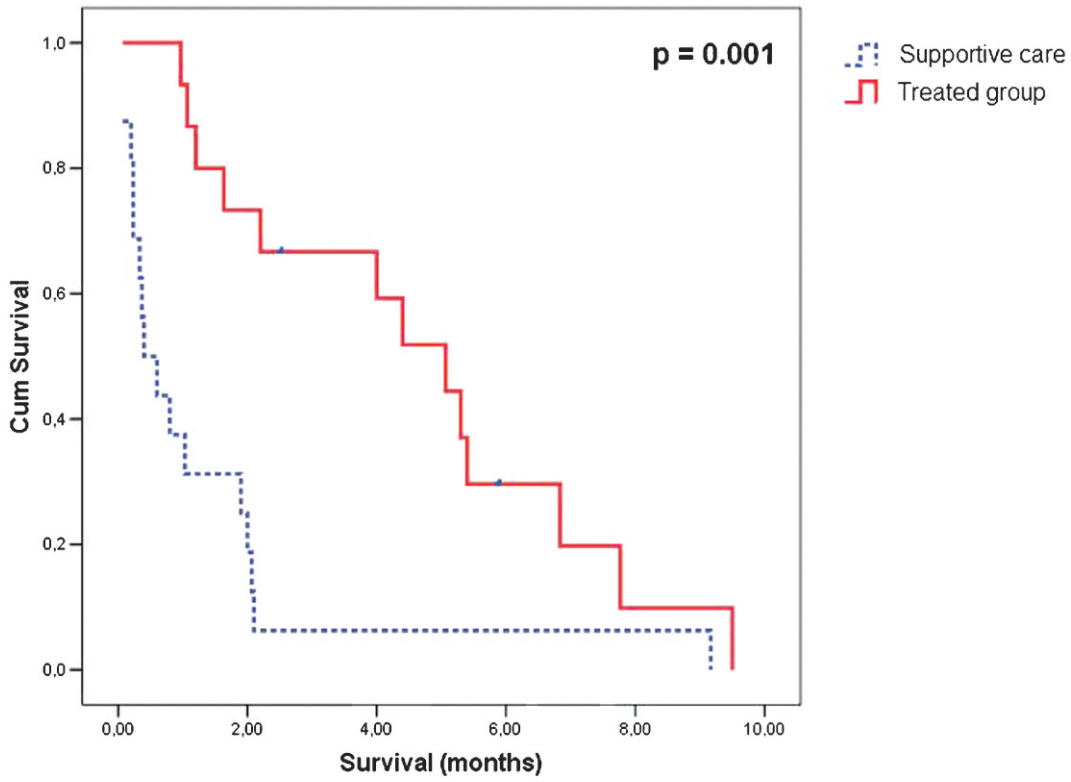


**Figure 1 -** Overall survival time of elderly AML patients according to patient group, 2003-2008.

## DISCUSSION

The results confirm the unfavorable prognosis of AML patients older than 60 years of age. The overall survival time was 2.9 months, and patients selected to receive intensive cytotoxic treatment or an alternative treatment (adapted ETI) experienced significant increases in overall survival time compared with patients who received supportive care only. However, the survival times described in this study are inferior to those reported in developed countries.[1,2] This phenomenon may be attributed to both socioeconomic differences and characteristics of the Brazilian national public health system. Brazil was one of the first countries in Latin America to make universal access to free health care a constitutional right, and the available services range from primary care to highly technologically complex treatments.[12] Nevertheless, this system has not been fully implemented, and patients wait a long time for access to specialized services.[13] This delay is particularly experienced by patients waiting to access the limited number of specialized hematology centers. The optimal management of AML and other hematological malignancies[14] necessitates a prompt diagnosis and the initiation of treatment without delay.

A number of new chemotherapy agents are under investigation in older patients with AML, such as DNA methyltransferase inhibitors (e.g., decitabine) and the purine nucleoside analog clofarabine. However, such drugs are not available via the public health services of developing countries, and alternative treatments are necessary for the management of elderly patients not suitable for intensive chemotherapy.

The Finnish Leukemia Group has proposed an alternative oral treatment composed of etoposide, 6-thioguanine and idarubicine that displays good response rates and an acceptable toxicity profile in advanced age AML patients.[8-10] The adapted ETI evaluated herein was associated with a significant increase in AML survival time and may be an alternative approach for the treatment of older patients who cannot participate in clinical trials.

The prevalence and survival times of AML in advanced age have not been adequately studied in Latin American countries. Beyríes et al. reported that Cuban AML patients older than 60 years of age experienced an overall median survival time of less than two months, and those selected to receive high-dose chemotherapy presented high rates of resistance and mortality.[15] A previous study conducted by our group showed that 33% of all AML cases occurred in patients who were older than 60 years of age, and the overall survival time was two months.[4] Moreover, no difference in overall survival time was noted between elderly AML patients who received intensive cytotoxic chemotherapy and those who received supportive care, suggesting that this group of patients should receive only palliative treatment. Five years later, our results indicate a historical improvement in the treatment of elderly patients with AML. This change can be attributed to a paradigm shift in the selection of therapeutic modalities coupled with improved medical and nursing training and better medical support. Despite the improvement in the overall survival of these patients, there was no difference in the hospitalization rate between the patient groups.

The impact of treatment guidelines adapted to local resources is exemplified by the initiative of the International Consortium on Acute Promyelocytic Leukemia (APL)[16] to improve the response and cure rates and reduce the mortality associated with APL treatment in developing countries.

The low number of patients enrolled in our study could be interpreted as a limitation, and a larger number of AML cases are currently being followed by our hospital to confirm our findings.

In conclusion, as part of the ongoing search to enhance the quality of health care and with all limitations of a single institution in the Brazilian public health system, we implemented a medical assistance approach that showed benefits for the management of AML patients. The treatment of AML in advanced age is challenging, and some patients may benefit from treatment with intensive or alternative chemotherapy that is appropriate for their age, performance status, and cytogenetics. We believe that outcomes in elderly AML patients can be improved by better and faster access to specialized health services, consistent training of medical and nursing staff in all spheres of care and the development of therapeutic algorithms and planned solutions that are directed at and customized for different regional realities.

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