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Acute myeloid leukemia in elderly patients: clinical features and therapeutic outcomes

Ronald Sergio Pallotta Filho[1,2*], Karen Vasconcelos1, Davimar Miranda Maciel Borducchi[1], Vitor Augusto Queiroz Mauad[1], Antonio Turpin[1]

[1]Hospital Estadual Mario Covas, São Paulo, Brasil.
[2]Universidade Santo Amaro, São Paulo, Brasil.

ABSTRACT

OBJECTIVE

To describe the epidemiological profile of patients aged 60 years or older with AML treated at a referral hospital in the ABC region in Sao Paulo, Brazil, assessing the impact of the therapeutic strategy on the overall survival (OS) of this cohort.

METHODS

Descriptive retrospective cohort study evaluating patients treated at Mario Covas State Hospital (HEMCO), for a period of 8 years, divided into groups according to the applied therapy.

RESULTS

A total of 44 patients were evaluated. There were no significant differences in OS when groups of patients treated in an intensive and non-intensive way were compared. However, there was a strong tendency, in patients older than 70 years, to present better results when submitted to reduced doses of QT. Regarding mortality, in the first month it was slightly higher in the subgroup of intensive chemotherapy, reflecting mortality related to induction, but the values tend to be equal in the first year.

CONCLUSION

The results obtained allow us to know the epidemiological profile and the evolution of the treatment in elderly patients diagnosed with AML treated in a reference unit for acute leukemia in a developing country.

DESCRIPTORS

Acute myeloid leukemia, Prognostic factors, Epidemiology, Laboratory diagnosis, Treatment.

Corresponding author:
Ronald Sérgio Pallotta Filho.
Médico do Hospital Estadual Mario Covas (HEMCO) e docente na Faculdade de Medicina da Universidade Santo Amaro_UNISA. Rua Prof. Enéas de Siqueira Neto, 340, São Paulo/SP, Brasil.
E-mail: rp.cohs@yahoo.com.br
ORCID ID: 0000-0002-9225-1290

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INTRODUCTION

Acute myeloid leukemia (AML) is characterized by clonal proliferation of immature cells derived from hematopoietic stem cells with subsequent replacement of normal bone marrow tissue. Its etiology is unknown, but some genetic lesions are implicated in its development. Cytogenetics, in the diagnosis of AML, is a well-defined prognostic marker. Chromosomal abnormalities characterized by balanced translocations, loss and gain of chromosomes are karyotypic changes peculiar to leukemias and are found in more than 65% of cases[1,2,3].

AML can occur in all age groups, representing about 80% of cases in patients over 18 years, but an important fact is that the average age at diagnosis ranges from 68 to 72 years, with approximately one third of patients older than 75 years[4].

According to the national policy for the elderly (PNI), law #8.842, January 4, 1994, and the statute for the elderly, law #10.741, October 1, 2003, define elderly as people 60 years of age or older. The World Health Organization (WHO) considers elderly the person aged ≥ 60 years in developing countries and ≥ 65 years in developed countries.

It must be recognized that chronological age is not an accurate marker for the changes that accompany aging, there are significant differences related to health status that must be considered in the assessment of the elderly cancer patient, this is the key to selecting and administering the most effective and safest therapy[5,6].

When the focus is AML there is no consensus as to which treatment strategy to adopt for patients older than 60 years4. The elderly with AML generally has a worse prognosis when compared to younger patients due to a higher incidence of comorbidities, higher rates of treatment-related mortality, and adverse features associated with the disease including a higher relapse rate[7]. In this age group, only 50% of patients will achieve a remission with standard induction therapy and long-term overall survival (OS) is less than 20%[8].

Chemotherapy protocols considered conventional are composed of anthracycline and cytarabine and can induce remission in up to 70% of patients aged <60 years and in 30% to 50% of older patients. In the latter group, aggressive treatments are associated with significant mortality and morbidity, often requiring prolonged hospitalization. Furthermore, conventional protocols may not be the most appropriate option for elderly patients with poor "performance status", severe comorbidities, or poor bone marrow reserve[9-11].

That is why it is important to individualize the treatment protocol, knowing the patient's health situation in a holistic way, especially in the elderly[2]. One way to know the patient's health status is through the Charlson Comorbidity Index (CCI), a method that uses selected clinical conditions recorded as secondary diagnoses to calculate the risk of death. The index calculates the patient's morbidity burden, regardless of the primary diagnosis.

In this study, the authors propose to evaluate elderly patients with AML treated in a public service focusing on their clinical characteristics and the different therapeutic strategies applied. The primary objective of this study was to describe the clinical and epidemiological characteristics and the overall survival (OS) of patients aged 60 years or older with AML followed at Hospital Estadual Mario Covas (HEMCO), which is characterized as a 100% public service, a reference in the treatment of acute leukemias in a developing country. The secondary objective was to evaluate the SG and mortality rate according to treatment protocols performed.

METHODS

This is a descriptive historical cohort study, where patient data were obtained from the electronic medical records, and the study was entirely developed at the institution itself. We included elderly patients (defined in this study as 60 years of age or older), with AML, diagnosed and treated at the Hematology Service of HEMCO for a period of 8 years from 2009. Individuals younger than 60 years and those older than 60 years initially treated in other services were excluded. Although the study included patients with AML secondary to myelodysplastic and myeloproliferative syndromes, those with chronic myeloid leukemia (CML) in blastic crisis and patients with acute promyelocytic AML were excluded because they were considered as a subgroup with distinct diagnosis and prognosis.

As for therapy, intensive chemotherapy included protocols based on high doses of anthracyclines (50 mg/m^2 daunorrubicin for 3 or 2 days) associated with 100 mg/m^2 cytarabine (for 7 or 5 days) and the VAM protocol (10 mg/m^2 cytarabine, 150mg/m^2 etoposide and 10mg/m^2 mitoxantrone). The non-intensive protocols were low dose subcutaneous cytarabine (20mg/m2 dose for 5 to 14 days), hypomethylating agents (azacitidine or decitabine) and hydroxyurea monotherapy. All patients received antibacterial prophylaxis with quinolones, antifungal prophylaxis with fluconazole and antiviral prophylaxis with acyclovir during the period of neutropenia.

Statistical significance was considered for p-values <0.05, using the chi-square test. Survival curves were estimated by the Kaplan Meier method and statistical comparison between them, when necessary, was made by the log-rank test for significance determination and Hazard Ratio for effect measurement. Subgroup analysis will be represented by a Forest Plot graph.

This study was submitted and approved by the Research Ethics Committee of FM do ABC/HEMCO, CAAE 8257131700000.

RESULTS

A total of 44 patients were analyzed, of these 20 received intensive chemotherapy by traditional protocols and 24 received low-dose chemotherapy (18 low-dose cytarabine and 6 hydroxyurea). The clinical and epidemiological characteristics are described in Tables 1 and 2.

Table 1. Clinical-epidemiological characteristics of patients with AML > 60 years treated at Hospital Estadual Mario Covas (HEMCO).

	Chemotherapy low dose n= 24	Intensive Chemotherapy n= 20
Age		
Age ≤ 70 years	4	12
Age > 70 years	20	8
Average - years	75,5	69,05
Gender		
Female	13	12
Male	11	8
Karyotype (Kt)		
Favorable	0	0
Intermediate	10	12
Adverse	4	2
Unknown (no metaphases or not collected)	10	6
Charlson Comorbidity Index	3,42	3
Hemoglobin (Hb)		
Hb > 12	2	0
Hb >10 e ≤ 12	1	3
Hb >7 e ≤ 10	12	14
Hb ≤ 7	9	3
Platelets		
Platelets > 150,000	1	3
Platelets >100.000 e ≤ 150.000	2	1
Platelets >50,000 e ≤ 100,000	4	3
Platelets ≤ 50.000	17	13
Leukocytes		
Leukocytes ≤ 10,000	10	7
WBCs >10,000 and ≤ 30,000	8	5
WBC >30,000 and ≤ 100,000	5	6
Leukocytes > 100,000	1	2
% Blasts	42,99	58,87

Cause of Death		
Recurrence	2	4
Disease Progression	15	3
Infectious	6	10
Other	1	3
Type of Acute Myeloid Leukemia (AML)		
New	12	17
Secondary	12	3
Response to Treatment		
Complete Response	2	8
Unable to assess (early death)	10	8
No response	12	4
Presence of CD34		
Presence	17	10
Absence	7	7
Unknown	0	3

Table 2. Karyotype of patients with AML > 60 years at Hospital Estadual Mario Covas (HEMCO).

Prognosis	Cytogenetic Alteration	Frequency
Favorable	-	0
Unfavorable	complex karyotype	4
	t(3;3)	1
	del 5	1
Intermediate	normal karyotype	18
	-y	1
	+8	1
	+6	1
	t(11;19)	1
	t(9;11)	1

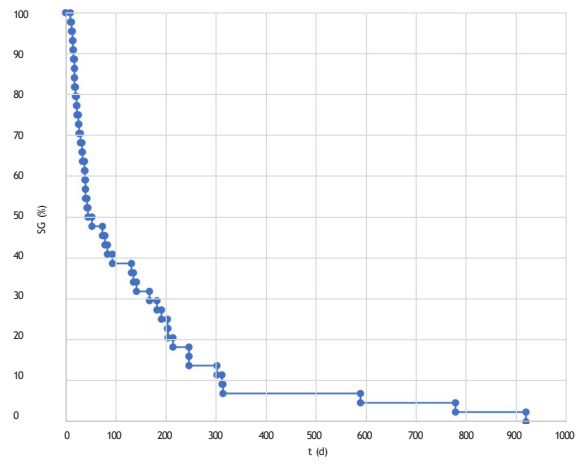
* In some intermediate karyotypes, there was more than one associated change.

The average Charlson Comorbidity Index (CCI) was 3.21 points. In the group of patients treated with intensive chemotherapy the average ICC score was 3, in the group treated with low-dose chemotherapy the average score was 3.42, showing that patients who did not undergo intensive QT had more comorbidities.

Regarding the presence of CD34, an unfavorable prognostic indicator, CD34 was found in 27 patients (61.4%) and in 14 patients (31.8%) this marker was negative. It is worth noting that in 3 patients (6.8%) it was not possible to find immunophenotyping data.

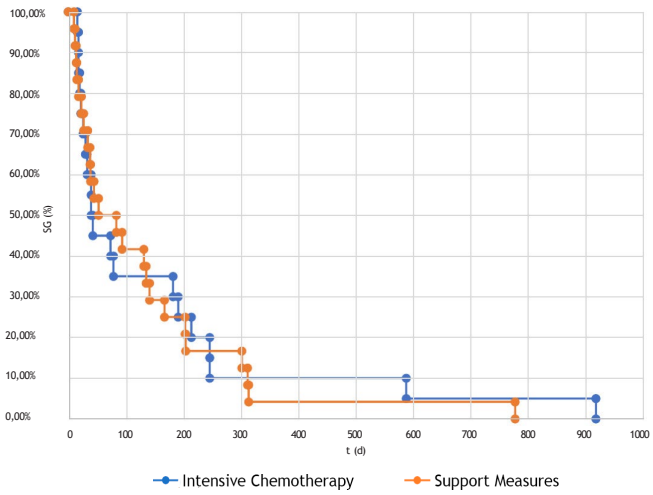
As for the response to treatment, 10 patients (22.72%) achieved complete remission of the disease, and in 18 of them (40.9%) it was not possible to evaluate the response because they died within the first 30 days after starting treatment. In 16 patients (36.4%) there was no response to treatment. The mean overall survival in days, considering the 44 patients, was 143 days, with a median of 49 days (Figure 1).

Figure 1. Overall survival at month 1 and year 1 of treatment in the general population, median 49 days, with month 1 being 68.2% and year 1 being 6.8%.



Determining the type of treatment performed, in the group treated with intensive chemotherapy (45.45%) the overall survival was 153 days, in the group treated with low-dose chemotherapy (54.54%) it was 133.5 days. The Kaplan-Meier curves for each of these variables can be seen in Figure 2.

Figure 2. Overall survival according to the intensity of chemotherapy performed.



Among the causes of death in patients, 6 patients (16.6%) died due to disease relapse, 18 of them (40.9%) due to disease progression, 16 of them (36.4%) due to infectious tails, and 4 of them (9.1%) due to other causes (2 due to bleeding, 1 due to pancreatitis, and 1 due to cardiogenic shock). Table 3 shows the causes of death stratified according to treatment regimen performed and Figure 3 the mortality in the first year.

Table 3. Causes of death stratified according to treatment regimen performed.

	Relapse	Progression	Infectious	Other
Intensive QT	4	3	10	3
Low-dose QT	2	15	6	1

Figure 3. Mortality in the first year.

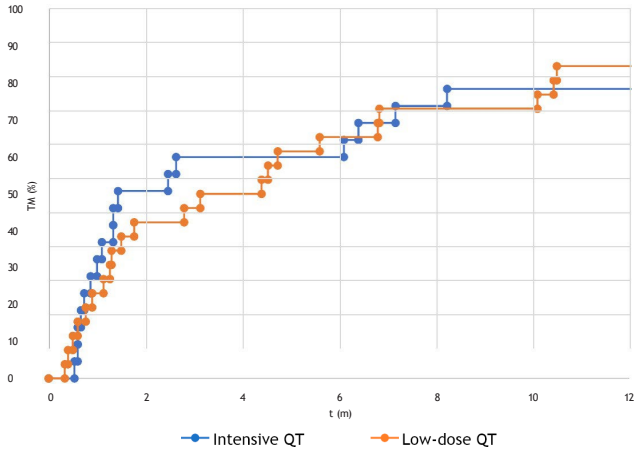
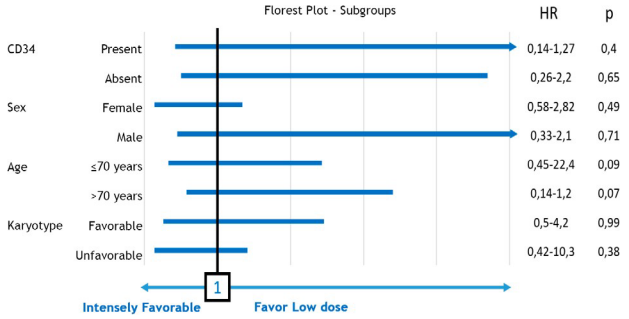


Figure 4. Florest Plot: overall survival in days stratified according to clinical and demographic characteristics of the patients.



Mortality in the first month was 35% in the group receiving intensive QT and 25% in those receiving low-dose QT. Mortality in the first year of treatment was 85% in the group receiving intensive QT and 91% in those receiving low-dose QT (p=0.9). Separate SG by variable was also estimated, as shown in Figure 4.

DISCUSSION

As for the clinical and epidemiological characteristics, a slight predominance of females in both groups was observed regarding the biological sex. Regarding age, the mean age of the intensive chemotherapy group (69.05 years) was lower than that of the low-dose chemotherapy group (75.5 years). It was also found that in this group undergoing intensive treatment the ICC scores were higher (3.2 x 3), meeting the data in the literature that define the greater the burden of comorbidity the lower the intensity of chemotherapy to be performed. This association is easy to understand, since protocols with more aggressive chemotherapy in inducing remission require prolonged hospitalization and supportive care that are costly and painful, in addition to an early mortality rate ranging from 17% to 54%. With higher morbidity and mortality, the reluctance to intensive treatment in a patient with a higher number of comorbidities is understandable and common, justifying this study bias.

Unfortunately, data regarding the degree of functionality and frailty of the elderly, which would be important tools for treatment definition, could not be collected in this retrospective cohort. Even the ECOG, an oncology score, data were only available for 10 patients. Older adults with low performance status (ECOG 04/03 regardless of the cause) have a higher treatment-related mortality rate and a lower likelihood of benefiting from intensive care, so these data are of fundamental importance to be present in the patient's chart upon hospital admission[3, 14, 15, 16].

As for the cytogenetic prognosis, when we analyze the distribution of karyotypes among the groups it becomes evident the large number of people allocated to the intermediate risk category (Tables 1 and 2). This is due to the frequent finding of normal karyotype, although we now know that these cases require additional research for mutations such as FLT3, NPM1, CEBPA and others for correct risk stratification. Thus, the limitations of a retrospective study such as this one is clear, since a large part of the intermediate group may have a favorable or unfavorable prognosis. The evaluation of the molecular prognosis should be the target of a specific study. Regarding cytogenetics, we did not have patients with favorable karyotypes, and complete remission was observed in 31.81% of the intermediate karyotypes and 16.6% of those considered to have unfavorable alterations[14, 17-20].

In this analysis, we chose to include secondary disease to show the high frequency of secondary AML in the elderly population. The medical literature shows a frequency of secondary AML in the elderly of 24% to 56%, compared to a prevalence of 8% in younger patients, according to the Medical Research Council AML study. Our study demonstrated a frequency of secondary AML of 34.1%, corroborating the literature data[1,3,4,12,14].

In our study, the complete remission (CR) rate was 22.72% among the 44 patients treated. When we evaluated the intensively treated patients, 40% of them achieved CR compared to only 8.33% of patients treated with low-dose chemotherapy achieving remission. Studies show that adults under the age of 60 treated with an induction regimen consisting of anthracycline combined with cytarabine have a 65% - 73% chance of achieving complete remission, while those over the age of 60 have between a 38% - 62% chance of achieving CR[21-23].

The analysis of the percentages of deaths at the beginning of treatment (first 30 days following induction therapy) had the primary objective of checking for differences in toxicity between the different treatment protocols. We observed that among the 20 patients treated intensively, 40% died at the beginning of treatment. As for the patients treated with low-dose chemotherapy, 41.6% of them died at the beginning of the treatment. In both arms a high early mortality rate was observed. International studies including patients of all ages usually report an early death rate of 15 to 20%[1,3,4,12,14,15].

We can note that this important difference found reinforces the need for a differentiated approach for elderly patients with AML considering their suitability for treatment based on PS, comorbidities, and age. A mortality rate around 40% of patients in both groups at the beginning of treatment reflects a failure in our health system and the lack of attention to our SUS dependent population, the most socio-economically vulnerable stratum.

The literature has shown that the SG of the elderly with AML has improved significantly over the last 4 decades, from only 1-2% in the 1980s to almost 20% today. This improvement can be attributed to many different factors, but when we evaluated the overall survival at 1 year in our population it was 10% in the intensively treated patients and 4.3% in those treated in a non-intensive manner, the same as reported in the international literature. No statistically significant differences were observed when we evaluated these groups. It is possible that factors related to our patients, such as nutritional status, immunological status, comorbidities, and late referral to the Service help explain this difference. In intensive care patients, death usually results from multiple organ failure due to infection, with the lung being the most affected primary site. In patients treated non-intensively, death occurs mainly due to disease progression[21-25].

Subgroup analyses did not show significance in overall survival, but there was a strong tendency in patients older than 70 years to obtain better results with reduced-dose QT.

Mortality was slightly higher in the first month in the intensive chemotherapy group, reflecting induction-related mortality, but values tended to equalize by the first year.

Despite all the limitations of a historical cohort, it is important to note that most studies of AML treatment involve younger populations, raising the question of whether the same results would still be valid if applied to an older population. This fact highlights the problem of elderly patients not being routinely incorporated and represented in clinical trials[24,25].

Unfortunately, most elderly people who develop AML will still die from their disease, so there are opportunities for improvement. Recently reported trials of new low-intensity treatment combinations using hypomethylating, or low doses of arabinoside C, in combination with venetoclax or vadastuximab have shown great promise, while the experimental drug CPX-351 leads to better results with intensive induction for certain high-risk patients24,25. However, access to such therapies for SUS patients is still uncertain.

CONCLUSION

The results obtained in this historical cohort study allowed us to know the epidemiological profile and the evolution of the treatment of elderly patients diagnosed with AML in a specialized unit of a developing country. No statistically significant differences were observed in the GS when evaluating the groups of patients treated intensively and non-intensively, but it seems essential to have access to the degree of functionality and frailty of the elderly to define the treatment. As for mortality, it was slightly higher in the first month for the intensive chemotherapy group, reflecting induction related mortality, but the values tend to equalize in the first year. The results provide little known information,

but necessary to health professionals to promote better care to these patients serving as a basis for the formulation of future prospective research.

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