DOI: 10.46765/2675-374X.2023V4N3P214

CHALLENGES TO ACHIEVING BMT IN THE TREATMENT OF AML IN BRAZIL: BAHIA UNIVERSITY HEMATOLOGY CENTER EXPERIENCE

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Received: 04 Dec 2023 • Revised: 12 Dec 2023 • Accepted: 21 Dec 2023.

ABSTRACT

Introduction: Acute myeloid leukemia is a heterogeneous aggressive leukemia with a poor prognosis. The standard remission induction regimen for medically eligible patients consists of a backbone of cytarabine & anthracycline.

Objective: This study assessed the efficacy and safety of cytarabine and anthracycline in a public health center in Salvador, Brazil.

Methods: It is a retrospective analysis of 45 non-promyelocytic AML patients diagnosed between 2018 and 2022. Subgroups analyzed included patients having FTL3 and NPM1 mutations, leukocyte count (>10,000 or <10,000), platelets count (>20,000 or <20,000), and transplanted patients. Kaplan-Meier methods were used to determine overall survival (OS) and progression-free survival (PFS).

Results: The median age at diagnosis was 43 years (16-69 years), and 62% were females. FLT3-ITD and NPM1 mutations were found for 17.8% and 13.3% of patients, respectively. 85% of the patients had a normal karyotype. For efficacy, 52% of patients were eligible for the next treatment after complete remission. Refractory patients were 20%. Early mortality was 28.8%. Median values of PFS and OS were 3.6 and 8.2 months, respectively. Patients presenting FLT3 mutation and stem cell transplantation had PFS and OS of 20 and 43 months, respectively.

Conclusion: The outcomes were consistent with the literature. Waiting time was not critical for treatment outcomes.

Keywords: Leukemia, Myeloid, Acute. Survival rate. Progression-Free Survival.

INTRODUCTION

Acute myeloid leukemia (AML) is characterized by infiltration of bone marrow, blood, and other tissues by proliferative and undifferentiated cells of the hematopoietic system[1,2]. Although the treatment of AML significantly improves outcomes for younger patients, the prognosis for the elderly remains poor: approximately 70% of patients aged 65 years and older die within one year of diagnosis. The National Cancer Institute (INCA) estimates that for the 2023-2025 triennium, 11,540 new cases of leukemia will be diagnosed, corresponding to 5,33 per 100,000 inhabitants in Brazil [3–5].

The disease prognosis is fundamental for its management. Prognostic factors are improved by stratifying patients according to treatment risk resistance or treatment-related mortality (TRM), in addition to the therapeutic decision, whether to use induction, consolidation or stem cell transplantation. Among clinical factors, increasing age and poor performance status are related to lower complete remission rates (CR) and decreased overall survival (OS) [2,3].

The first stage of AML treatment involves the concept of eligibility for intensive induction chemotherapy and aims for complete remission (CR). Furthermore, three therapeutic modalities can be administered to AML patients in post-remission: conventional-dose chemotherapy, high-dose chemotherapy (consolidation) followed by salvage with autologous hematopoietic stem cells, and allogeneic hematopoietic stem cell transplantation [2,5,6]. Therapies have remained essentially the same for 40 years. The therapeutic regimen, known as "7+3", is performed during the induction period of treatment for eligible patients [1,2]. However, most patients achieving CR with a 7+3 regimen eventually relapse[1].

This study aims to evaluate the efficacy and safety of treatment induction with anthracycline and cytarabine (7+3 regimen) in patients diagnosed with Acute Myeloid Leukemia in a public hospital unit in Salvador/Bahia for five years. In addition, we plan to correlate efficacy and early mortality with treatment waiting time, which is unprecedented in Brazil.

METHODS

The present work was submitted to the Research Ethics Committee of the Hospital Universitário Edgar Santos (HUPES). Retrospective patient data were analyzed up to 01/19/2023.

This is a retrospective hospital-based cohort study evaluating the efficacy and safety of 7+3 chemotherapy treatment (anthracycline + cytarabine) in patients diagnosed with non-promyelocytic Acute Myeloid Leukemia between 2018 and 2022 at the University Hospital Professor Edgar Santos - HUPES, in the city of Salvador/Bahia. Data collection was performed from physical and electronic medical records.

HUPES is a reference university hospital in the North/Northeast region of Brazil, encompassing a Bone Marrow Transplantation unit and offering, in partnership with scientific research, hematological tests not provided by the Unified Health System in Brazil (SUS). The hematological tests performed include FLT3 and NPM1 mutations, in addition to karyotype.

To analyze the efficacy of AML induction using anthracycline and cytarabine regimen, the following parameters were followed: (1) overall survival (OS - period between the initiation of therapy with 7+3 regimen and the date of possible death); (2) progression-free survival (PFS - period between the date of initiation of 7+3 therapy and the date of evidence of possible disease progression); (3) eligible for the next treatment (patients achieving complete remission after induction with 7+3 regimen and who underwent subsequent bone marrow transplant or consolidation therapy within 60 days). PFS and OS were analyzed through the Kaplan-Meier methodology, using the R project version 2.13.1 program for Windows.

The subgroups to evaluate the efficacy and safety of the 7+3 regimen were defined as (1) FLT3 or NPM1 patients mutation status; (2) total leukocytes at the time of diagnosis (less than/equal to or above 10,000); (3) total platelets at the time of diagnosis (less than/equal to or above 20,000); (4) patients who underwent bone marrow transplantation or not.

The p-value with a 90% confidence interval ($p = 0.01$) was adopted for statistical analysis between subgroups. Early mortality was defined as death occurring within four weeks after the first day of treatment. Waiting time was defined as the number of days patients diagnosed with AML had to wait until admission to HUPES.

RESULTS

Between 2018 and 2022, 45 patients underwent induction therapy with a 7+3 regimen at HUPES. The majority were female (62%), from the city of Salvador (26%), and brown-skinned (60%). The mean age was 43 years (16-69 years). The search for FLT3 mutation status was carried out in 30 (66.7%) patients; the majority belonged to the non-mutated group (48.9%;

Table 1). The NPM1 mutation search was performed in 25 (55.5%) patients; the rest were from the non-mutated group (42.2%). A Karyotype exam (85% had a normal karyotype) was performed in 14 patients. The characteristics of the patients are shown in Table 1.

TABLE 1. Characteristics of patients treated with 7+3 regimen in HUPES (N=45).

	Number of patients (%)
AGE > 60 years < 60 years	 5 (11.1) 40 (88.9)
GENDER Female Male	 26 (62.2) 17 (37.8)
RACE White Black Brown	 11 (24.5) 7 (15.5) 27 (60)
Nationality Salvador Bahia State Other	 12 (26.7) 30 (66.7) 3 (6.6)
FLT3 Status Mutation No-Mutation Unknown	 8 (17.8) 22 (48.9) 15 (33.3)
NPM1 Status Mutation No-Mutation Unknown	 6 (13.3) 19 (42.2) 20 (44.5)
Leukocytes* > 10 x 109L < 10 x 109L	 30 (66.7) 15 (33.3)
Platelets* > 20 x 109L < 20 x 109L	 32 (71.2) 13 (28.8)
Transplantation** Yes No	 8 (17.8) 37 (82.2)

*At the time of diagnosis, **Allogeneic related/unrelated (7) and haploidentical (1) bone marrow transplantation.

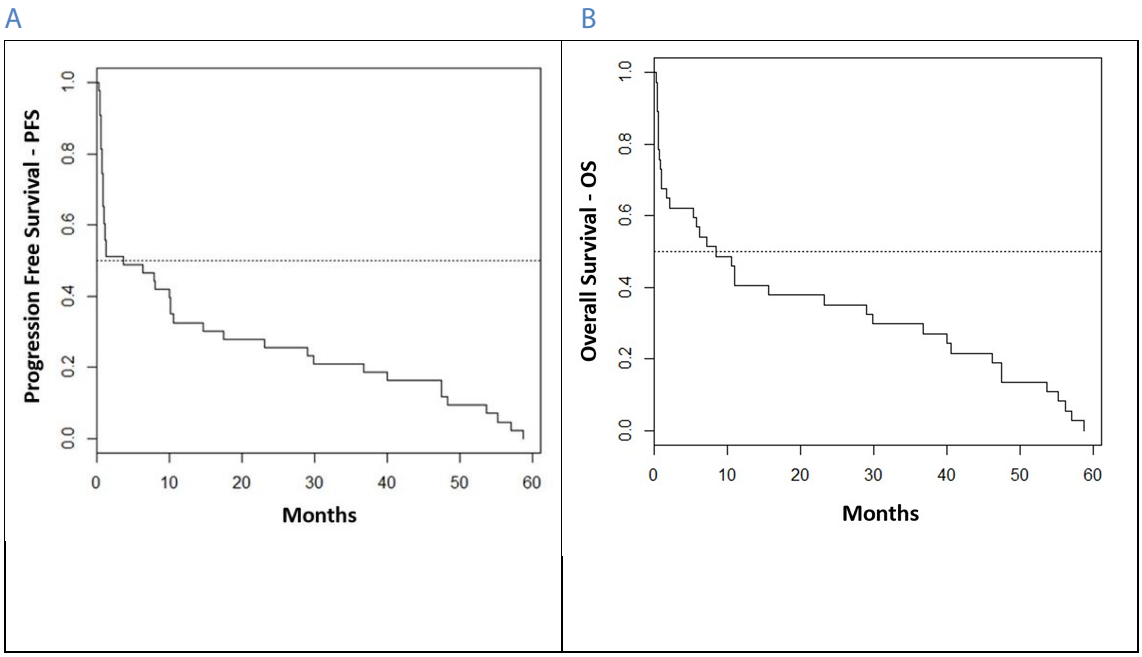
The mean waiting time for those patients who required hospitalization to start treatment with 7+3 regimen was 12.3 days (Table 2). There was no difference in the mortality for patients waiting less than 12.3 days or more. Five patients out of 38 died irrespective of waiting time (Table 2).

TABLE 2. Early mortality according to waiting time for treatment initiation.

Less than 12.3 days (%)	More than 12.3 days (%)
5 (38)	5 (38)

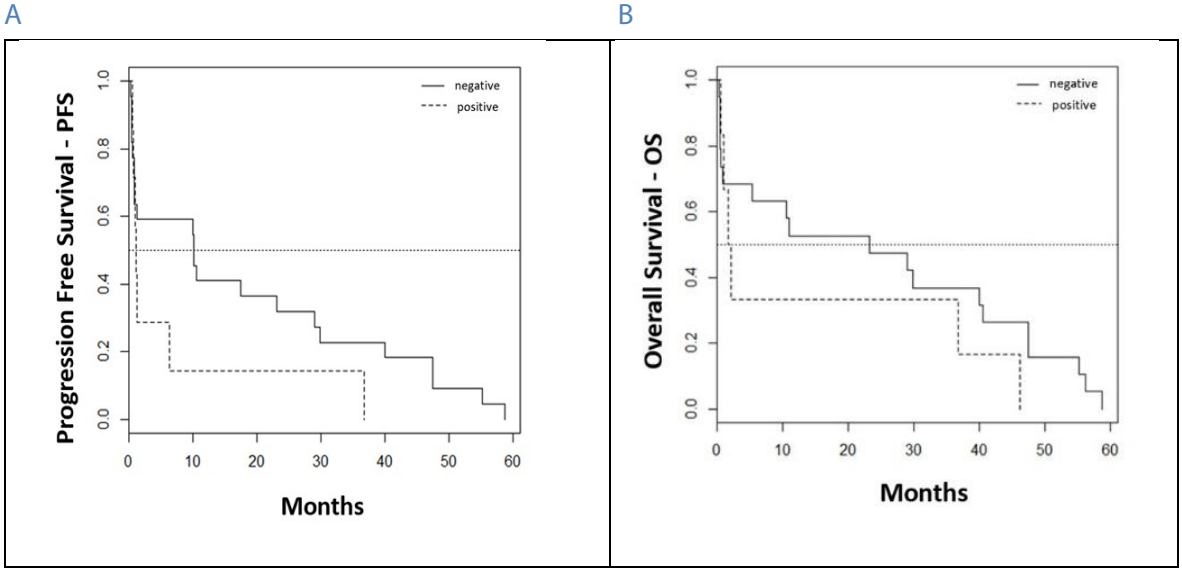
Regarding efficacy, 52% of the patients were eligible for the next therapy after complete remission (consolidation or stem cell transplant), and 20% did not respond to treatment. Early mortality (within four weeks) was 28.8%, and the causes of death were septicemia (8), alveolar hemorrhage (2), tension pneumothorax (1), acute respiratory infection (1), and COVID-19 (1). Median PFS and OS were 3.6 and 8.2 months, respectively. Early mortality was not affected by waiting time for treatment initiation (Figure 1 and Table 2).

FIGURE 1. Kaplan-Meyer curve for progression-free survival (A) and overall survival (B) in AML Patients treated with a 7+3 chemotherapy regimen.



FLT3 mutation-free patients had a median PFS of 10.1 months versus 1.1 months for FLT3 patients with mutation (HR 0.84; p=0.330; Figure 2A). The prognosis for OS was worse for FLT3 patients having the mutation, with a median of 1.9 months versus 23.3 months for those with no mutation, marginally significant (HR 0.63; p =0.077: Figure 2B).

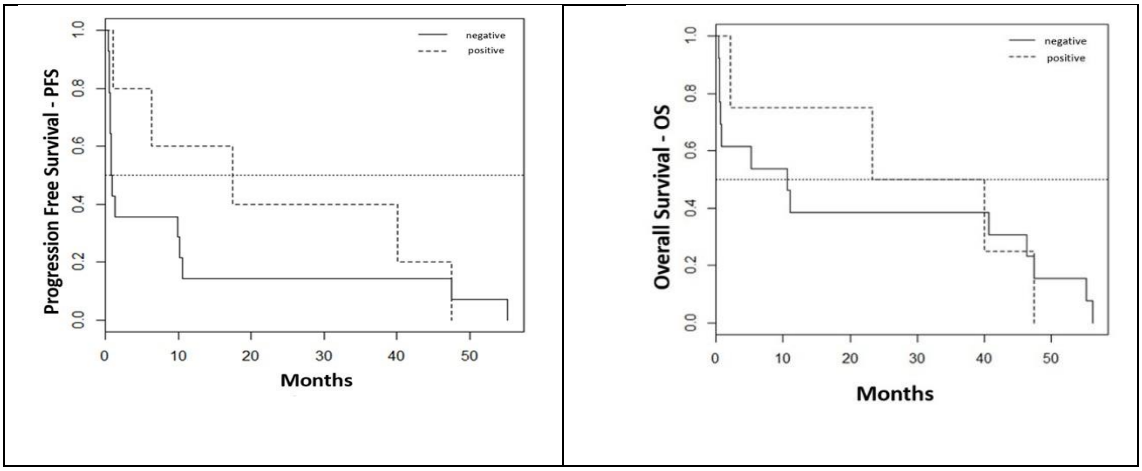
FIGURE 2. Progression-Free Survival (A) and Overall Survival (B) for FLT3 mutation in AML patients treated with 7+3 chemotherapy regimen.



Median PFS for NPM1-patients with mutation was 17.4 vs. 0.9 months for those with no mutation (Figure 3A). OS for NPM1 patients with mutation against those without mutation was 31.7 vs. 10.6 months (HR 0.99; p = 1.00). See Figure 3B.

FIGURE 3. Progression-Free Survival (A) and Overall Survival (B) for NPM1 patients with an AML mutation treated with a 7+3 chemotherapy regimen.

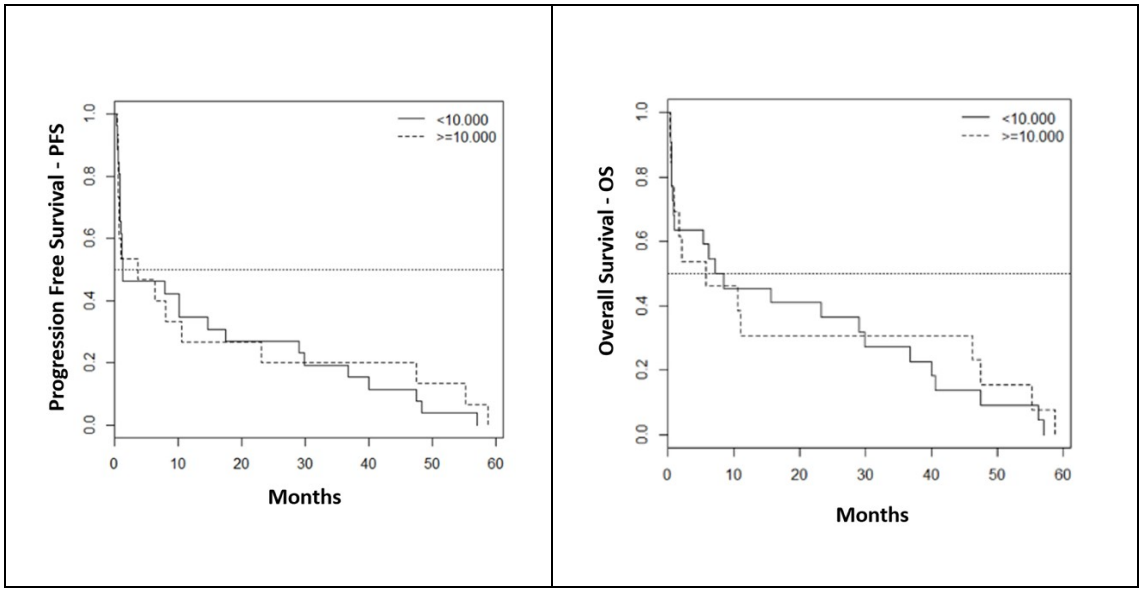
A B



The median for PFS was higher in the group of patients who had leukocytes above 10,000 at the time of diagnosis compared to the group of leukocytes below 10,000 (3.64 vs 1.24; HR 0.91; p = 0.78). There was also a better prognosis regarding OS (7.8 vs. 5.7; HR 0.85. p = 0.67). See Figure 4A and B.

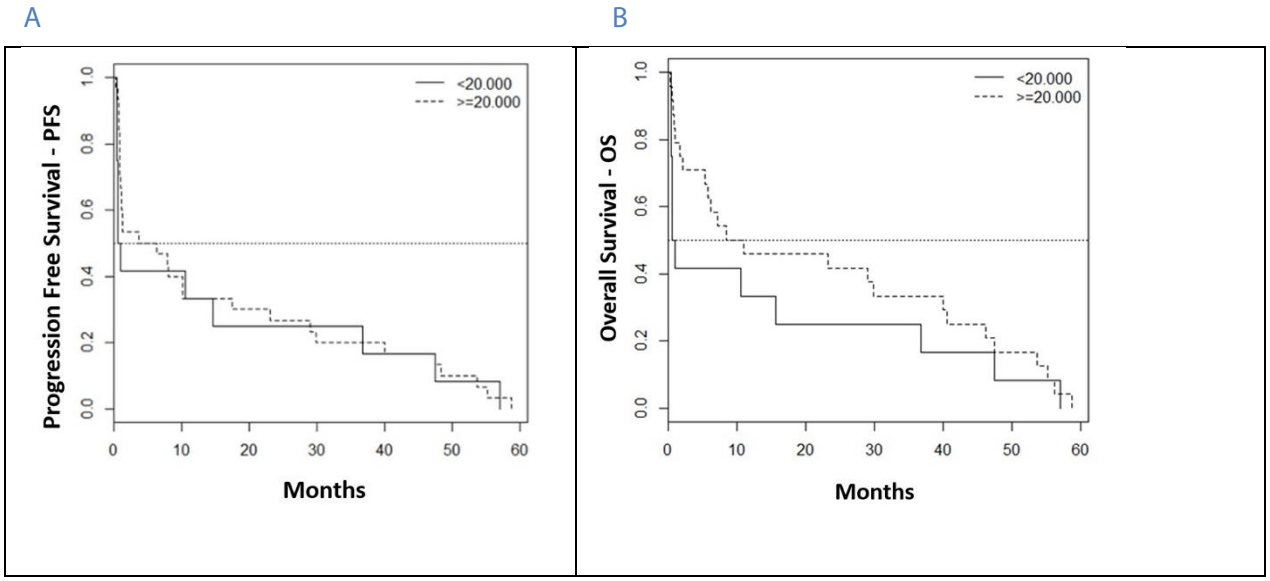
FIGURE 4. PFS (A) and OS (B) related to the number of leukocytes at AML diagnosis in patients treated with a 7+3 chemotherapy regimen.

A B



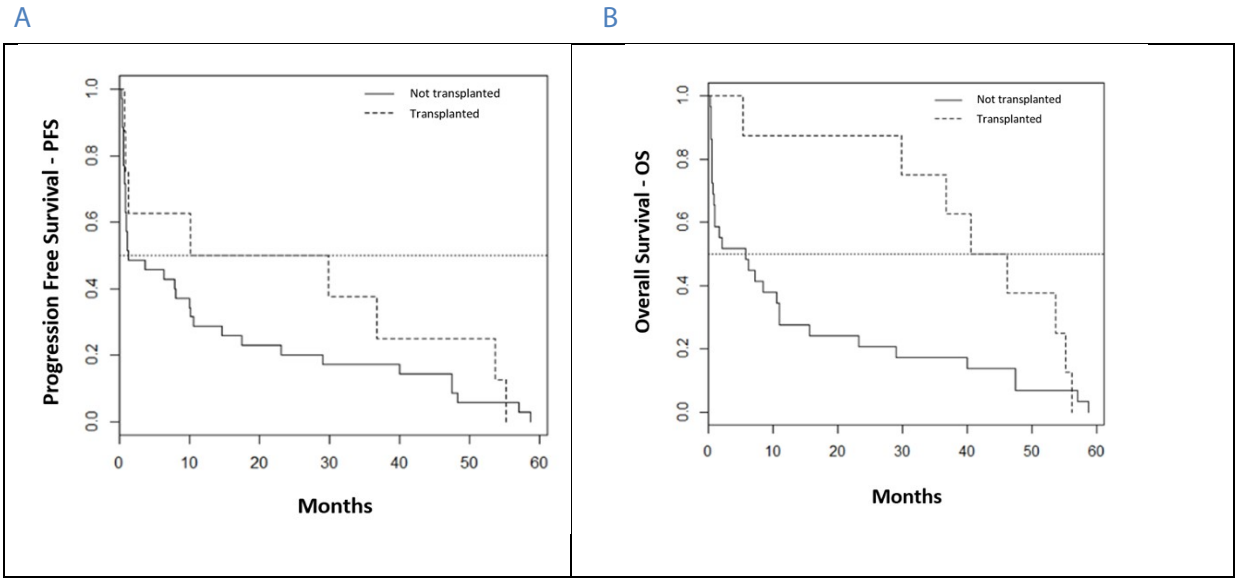
Regarding the number of platelets at the time of diagnosis, a better prognosis was observed for the group that had platelets greater than 20,000, both for median PFS (5.0 vs. 0.6 months; HR 0.81; p = 0.540) and median OS (9.7 vs. 0.9 months; HR 0.68; p = 0.27). See Figure 5A and B.

FIGURE 5. PFS (A) and OS (B) related to the number of platelets at AML diagnosis in patients treated with a 7+3 chemotherapy regimen.



Patients eligible for the next treatment and who underwent bone marrow transplantation had a higher PFS (20.0 vs. 1.2 months; HR 0.67; p = 0.310) and a statistically significant OS (43.5 vs. 5.7 months; HR 0.47; p = 0.065), as seen in Figure 6A and B.

FIGURE 6. Patients PFS (A) and OS (B) for AML treated with 7+3 chemotherapy regimen in relation to bone marrow transplantation.



DISCUSSION

The efficacy and safety outcomes of this study using a 7+3 chemotherapy regimen demonstrated that 52% of the patients were eligible for the next treatment (complete remission), the median progression-free survival was 3.6 months, and overall survival 8.2 months, including early mortality of 28% (61% due to septicemia). Significant treatment efficacy among the groups studied included higher OS (85%) for transplanted versus non-transplanted patients, and patients having an FLT3 mutation had significantly worse OS (90% higher). The mean waiting period to start treatment (12 days) was not a critical factor for clinical outcomes.

Our results are consistent with other real-life studies in Brazil involving AML. A 10-year study observed a complete remission rate of 53% and an early mortality of 20% for treated patients. The median OS was 7 months[7]. A retrospective study at a public service in Minas Gerais[8] found a median OS of 3.7 months and early mortality of 37%. In São Paulo, two similar studies in different public institutions reported complete remission of 49.5% and early mortality of 25.8%[9], including a median overall survival of 4.6 months[10]. Another multicentric retrospective study in Brazil found a median OS of 12.4 months[11]. A complete remission of 62% involved another study, and 15% of patients were alive at an estimated time of 13 years[9,12].

Bone marrow transplantation (BMT) is indicated as standard post-induction treatment after a 7+3 regimen for patients with intermediate or unfavorable cytogenetic risk. BMT is the most effective post-remission therapy for AML and is particularly highly recommended worldwide for patients aged 45 to 59 years and/or with high-risk cytogenetics. The efficacy and safety results of HUPES transplanted patients converge with data published for other real-life studies [3,7,11,13].

The 2022 ELN and the NCCN (version 3.2023) describe that FLT3-ITD mutations represent an unfavorable prognosis in patients with AML. The literature describes that patients with FLT3-ITD mutations have a poor prognosis, with an increased risk of recurrence and lower overall survival compared to patients without the mutation, similar to our study[13–15].

Leukocyte counts below 10,000 and platelet counts below 20,000, together with the absence of NPM1 mutation, had a worse prognosis for PFS and OS. However, they were not statistically significant in the present study. However, the European LeukemiaNet (2022) states that low leukocyte and platelet counts are associated with a higher mortality risk due to bleeding events and tumor lysis. In the same context, it is known that patients with NPM1 mutations (56%) have higher complete remission rates and higher disease-free and overall survival than wild-type NPM1 patients. NPM1 mutation (without FLT3 mutation) has a favorable prognostic factor in the context of AML [14,16].

Patients with hematologic malignancies are at increased risk of infection, associated with high morbidity and mortality. Patients with AML have qualitative and quantitative deficits in granulocytes, predisposing to bacterial and fungal infections [17]. Our real-life study for a developing country, involving socio-economic differences compared to developed countries, demonstrated that mortality data due to infections was the leading cause of death during induction with 7+3 chemotherapy.

HUPES patients waited, on average, 12 days to start treatment. To date, no Brazilian studies related the time to start AML treatment to clinical outcomes. However, a retrospective Swedish study found that patients aged up to 60 years waited between 11 and 15 days to start induction therapy and did not show significant disease remission, mortality up to 30 and 60 days, and overall survival at two years compared to those patients waiting between 0 and 5 days [18].

The combination chemotherapy regimen with anthracycline and cytarabine in eligible patients is standard for national and international guidelines. The National Comprehensive Cancer Network (NCCN), the European LeukemiaNet (ELN), and the Manual de Oncologia Clínica do Brasil (MOC) [19] recommend the induction of AML with the 7+3 regimen for eligible patients. The institutional protocol by the Hospital das Clínicas to treat patients with this type of leukemia is consistent with the leading global recommendations. However, for patients with the FLT3-ITD mutation, it is indicated (in Brazil – supplementary health, and in other international guidelines) the addition of midostaurin target therapy to the 7+3 regimen due to improved survival. However, SUS does not cover this treatment, and HUPES does not perform it. It is a high-cost therapy, and discussions of its incorporation into health services in Brazil are necessary. It is also observed that in some international protocols, such as NCCN, venetoclax treatment (BCL2 inhibitor) can be added for patients in AML induction therapy. This is not an approved indication in Brazil and is not performed at HUPES either [4,15,20] .

The study's advantages were the correlation of efficacy and early mortality with waiting time for treatment initiation in a public hospital in Brazil. Furthermore, it is the first time that data was collected in northeastern Brazil. The limitations include the statistical relevance of between-group comparisons, given that it was a retrospective study with a total population of 45 patients. For the statistical analysis between subgroups, the p-value with a 90% confidence interval ($p = 0.01$) was adopted, which is different from other studies with a higher population and p-value ($p = 0.05$).

Acute Myelocytic Leukemia is a disease with limited therapeutic options. Induction followed by consolidation therapy remains standard in the main therapeutic guides in onco-hematology settings. The efficacy and safety demonstrated in this work are consistent with the national and international literature. The waiting period for treatment does not seem to be a determining factor in clinical outcomes compared to other studies. Improvements in diagnostic processes, prevention of opportunistic infections, and developing new technologies for treating AML are vital.

ACKNOWLEDGMENTS

We would like to thank the Hospital Universitário Professor Edgard Santos in Bahia for all the support during the study.

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