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ORIGINAL ARTICLE

FLT3-MUTATED ACUTE MYELOID LEUKEMIA OUTCOMES IN A NORTHEAST BRAZILIAN UNIVERSITY HOSPITAL

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ABSTRACT

Mutations in the FMS-like tyrosine kinase 3 (FLT3) gene occur in approximately 25-45% of new diagnoses of Acute Myeloid Leukemia. The addition of FLT3 inhibitors to conventional protocols improves overall survival in this condition. Objectives: To assess the incidence of FLT3 gene mutation among patients diagnosed with AML at Walter Cantídio University Hospital; Describe access to FLT3 inhibitors and bone marrow transplantation (BMT), and the overall survival of this group. Methodology: Retrospective evaluation of medical records of patients treated for AML between 2020 and 2022. Statistical analysis was performed using the Kaplan-Meier method to estimate survival probability. Results: 47 patients were diagnosed with AML during this period, of whom 17% had FLT3+ mutation. 3/8 patients accessed FLT3 inhibitors. The median survival with FLT3+ mutation was 9.1 months vs. 12.9 months in FLT3- (p = 0.196). The overall survival of AML patients was 30.9% at 2 years. 11/47 patients underwent allogeneic BMT. Conclusion: The addition of targeted therapies and BMT may contribute to reduce mortality in AML. Elderly patients and those not undergoing HSCT have worse outcomes.

Keywords: Leukemia, Myeloid, Acute. Bone Marrow Transplantation. Genetics. Mortality.

INTRODUCTION

Acute Myeloid Leukemia (AML) is a neoplasm originating from hematopoietic stem cells, marked by aggressiveness, where medullary occupation by myeloid precursors leads to hematopoietic dysfunction and severe cytopenias. It typically manifests with dyspnea, asthenia, severe infections, and bleeding. International data estimate a median age of diagnosis of 65 years and an overall 5-year survival rate of approximately 24%[1].

Cytogenetic and molecular evaluation demonstrated significant heterogeneity among patients, due to recurrent mutations or germline predisposition, as well as acute leukemia secondary to myelodysplasia and therapy related.

Mutations in the FMS-like tyrosine kinase 3 (FLT3) receptor are the most frequent genetic alteration associated with AML[2], present in all FAB subtypes (more prevalent in subtype M3). This transmembrane receptor is located in CD34+ precursor cells with potential for myeloid and lymphoid differentiation and is activated through the FLT3 ligand (FL) expressed in cells of the tumor microenvironment. Its auto-

phosphorylation leads to the activation of multiple intracellular signaling pathways responsible for regulating apoptosis, proliferation, and differentiation.

Approximately 30% of AML cases exhibit abnormal expression of the FLT3 receptor. Mutations of the internal tandem duplication (ITD)[3] type result from an in-frame duplication in the juxtamembrane domain, as well as missense mutations of a single amino acid in the tyrosine kinase domain (TKD). These mutations lead to constitutive activation of the receptor and dysregulation of auto-inhibitory mechanisms, causing proliferative and survival gains through activation of the Ras and STAT5 pathways[4,5].

Epidemiological studies have shown that FLT3-ITD mutation is associated with a higher relapse rate, being an independent predictor of worse event-free survival (EFS) and overall survival (OS)[6]. These data supported the inclusion of this genetic marker as a defining intermediate risk factor[7], independent of allelic ratio. Its identification led to the development of targeted therapies, consisting of FLT3 inhibitors (e.g., sorafenib, midostaurin, gilteritinib, and quizartinib).

Randomized clinical trials demonstrated the efficacy of midostaurin (RATIFY trial)[8] and quizartinib (QUANTUM-FIRST trial)[9] inhibitors in newly diagnosed patients when added to intensive chemotherapy (daunorubicin and cytarabine). The ADMIRAL trial[10] showed the efficacy of gilteritinib monotherapy in relapsed and refractory patients, with or without previous exposure to FLT3 inhibitors.

MATERIALS AND METHODS

This is a descriptive retrospective observational study aiming to evaluate patients diagnosed with Acute Myeloid Leukemia (AML) treated in either inpatient or outpatient settings at the Hematology Service of Walter Cantídio University Hospital (HUWC-UFC).

Adults (aged 18 years or older at the time of diagnosis) diagnosed according to the European LeukemiaNet[3] criteria between January 1, 2020, and December 31, 2022, were evaluated.

Data collection was performed through chart review and consultation of the mortality registry. The project was approved by the Research Ethics Committee (CEP-HUWC) under approval number 6,177,086.

This work aimed to define the incidence of FLT3 mutation in this center, describe demographic data, access to bone marrow transplantation and FLT3 inhibitors, and conduct survival analysis of this population.

The R software (version 4.3.2) was used for statistical analysis and graph generation. Survival analysis employed the Kaplan-Meier method, and comparison was performed using the Logrank test.

RESULTS

During the period analyzed in this study, 65 cases of Acute Myeloid Leukemia (AML) were diagnosed. Of these, 18 were classified as Acute Promyelocytic Leukemia and were therefore excluded from the analysis.

The median age was 49.3 years (range: 18-76 years), with a predominance of females (57.4%). Most patients came from the countryside of the state of Ceará (55.3%). Hypertension, type 2 diabetes mellitus, smoking, and alcoholism were the most frequent comorbidities (see Table 1).

Regarding the characterization of AML, 70.2% of patients were classified as "Not otherwise specified[11], while 21.3% received the clinical diagnosis of "AML secondary to myelodysplasia" due to the lack of access to molecular markers for characterizing related mutations. There were also diagnoses of chronic myeloid leukemia in myeloid blast crisis (6.4%) and therapy-related AML (2.1%).

Using the risk classification established by the European LeukemiaNet in 2022, 70.2% of patients were classified as Intermediate risk, 10.6% as Favorable risk, and 19.1% as High risk.

Cytogenetic and molecular evaluation showed 17% of cases with FLT3 mutation (n=8, FLT-TKD = 1, FLT3-ITD = 7). The most frequent findings in the karyotype were deletion 7q, t(8;21), and complex karyotype. 12.8% of patients had a normal karyotype, and evaluation was not possible in 21.3% due to the absence of metaphase growth.

The median time between diagnosis and the start of treatment was 8 days (range 1 to 127 days). Most patients underwent induction with anthracycline-based regimens (76.6%) in the first line. Approximately 10% underwent supportive therapy. The complete response rate was 53.1% among these patients, with 17% dying during induction therapy.

Of the patients with FLT3 mutation (n=8), 3 accessed FLT3 inhibitors, as shown in the Swimmer plot (Figure 1).

Hematopoietic stem cell transplantation (HSCT) was performed in 23.4% of patients, with matched

sibling donors (54.5%), unrelated donors (18.2%), and haploidentical donors (27.3%). Most patients underwent reduced-intensity conditioning (54.5%). The main reasons for not transplanting were lack of sustained response (38.9%), therapy-related death (25%), and clinical contraindication (19.4%).

Disease progression was the main cause of death (83%), followed by infectious and hemorrhagic complications (34% and 11%, respectively). The early death rate (within 60 days after diagnosis) was 20.8%.

Overall survival of this patient group (Figure 2) was 51.1% at 1 year (CI 38.6-67.6%) and 30.9% at 2 years (CI 19.7-48.7%), with a median survival of 12.2 months (CI 7.6-22.7 months). Comparison between subgroups showed no statistically significant difference in survival (Figure 3) between mutated and non-mutated FLT3 (median of 9.1 vs. 12.9 months, $p = 0.49$). There was better survival (Figure 4) in patients under 60 years of age ($p = 0.004$) and those undergoing HSCT ($p = 0.0001$).

DISCUSSION

Acute myeloid leukemia (AML) continues to pose a significant mortality burden in low- and middle-income countries[12]. This study revealed complete response rates and survival times comparable to other Brazilian centers but notably lower than data from high-income countries[13,14]. Early mortality remains a challenge[15], with deaths primarily attributed to infectious complications and delayed access to specialized centers.

Access to bone marrow transplantation is another limiting factor for AML patient outcomes, with only 23.4% of patients able to undergo the procedure at this center. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the mainstay in treating patients with adverse and intermediate-risk AML[16]. Patients who underwent HSCT achieved a 2-year overall survival of 79.5%, demonstrating the efficacy of the procedure in this cohort.

The slow incorporation of new drugs within the public healthcare system also hampers outcome improvement[12]. In this study, we observe that recent advancements resulting from the approval of FLT3 tyrosine kinase inhibitors (FLT3-TKIs) have not been routinely incorporated, with access limited to 3 out of 8 patients with mutated FLT3.

Patients aged 60 years or older had significantly inferior outcomes, with a median overall survival of 1.4 months. This data is similar to previous decades and may be related to the limited therapeutic arsenal available within the Brazilian Unified Health System (SUS). At the time that this article was written, only low-dose cytarabine (LDAC) and hydroxyurea were provided as low-intensity therapies. Advances such as BCL-2 inhibitors, hypomethylating agents, and CPX-351[17] remain unavailable in the Brazilian public sector.

This study has limitations, including the short analysis period, lack of access to diagnostic tests and risk stratification (notably among patients with early death), as well as incomplete chart records due to its retrospective nature.

CONCLUSION

AML remains a high-mortality disease. Patients not undergoing allogeneic transplantation and elderly patients had worse survival in this center. Increasing access to new drugs, such as FLT3-TKIs, may improve its outcomes. Further epidemiological studies, encompassing other oncology treatment centers, are necessary to accurately describe the real-world scenario of this condition.

TABLE 1. Demographic data of patients diagnosed with non-promyelocytic acute myeloid leukemia at Walter Cantídio University Hospital, between 2020-2022

	N (%)
Age group	
18-29 years	9 (19,1)
30-39 years	9 (19,1)
40-49 years	6 (12,7)
50-59 years	14 (29,8)
60-69 years	8 (17)
70-79 years	1 (2,1)
Median age in years (range)	49,3 (18-76)
Sex	
Male	20 (42,6)
Female	27 (57,4)
Hometown	
Fortaleza	21 (44,7)
Other cities	26 (55,3)
Comorbidities	
Hypertension	11 (23,4)
Diabetes mellitus	9 (19,1)
Smoking	6 (12,7)
Alcoholism	6 (12,7)
Illicit drugs addiction	3 (6,4)
Obesity	2 (4,2)
Cardiopathy	2 (4,2)
Other neoplasia	1 (2,1)
No comorbidity	22 (46,8)
Classification	
AML, NOS	33 (70,2)
AML secondary to myelodysplasia	10 (21,3)
CML in myeloid blast crisis	3 (6,4)
Therapy-related AML	1 (2,1)

FIGURE 1: **Swimmer's plot of patients diagnosed with FLT3-mutated AML**

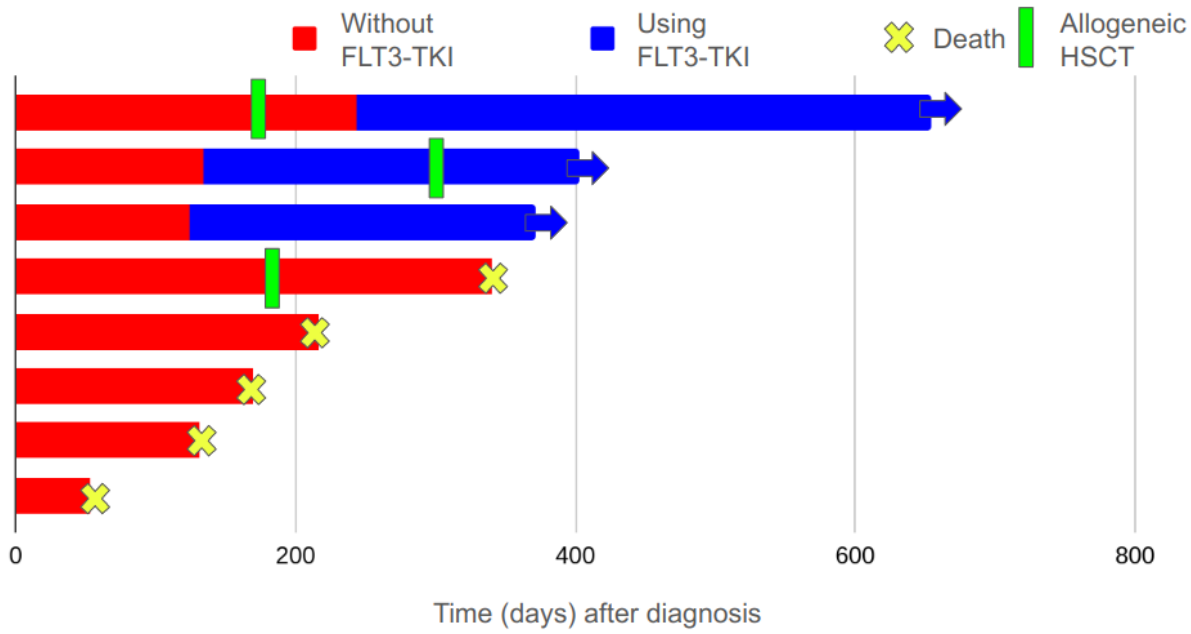


FIGURE 2: **2-years overall survival**

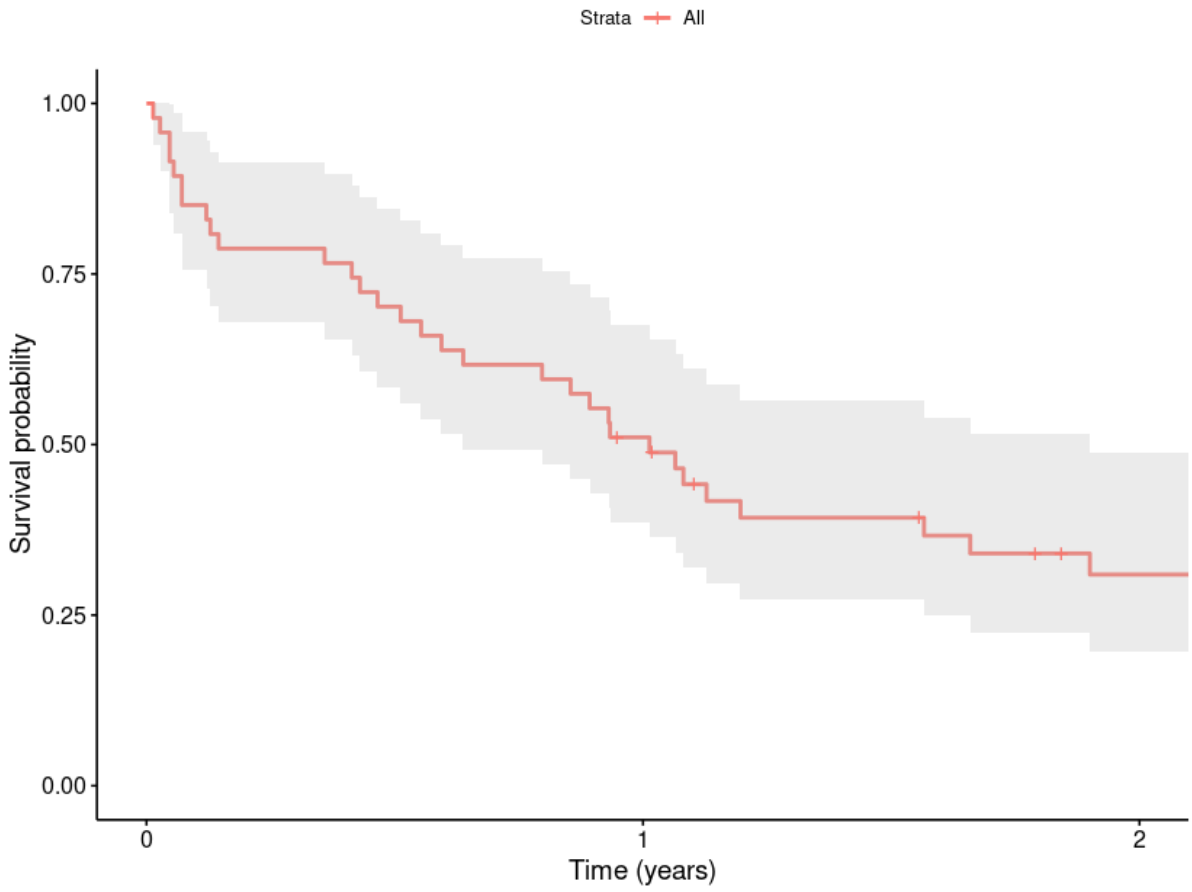


FIGURE 3: Overall survival by FLT3 mutational status

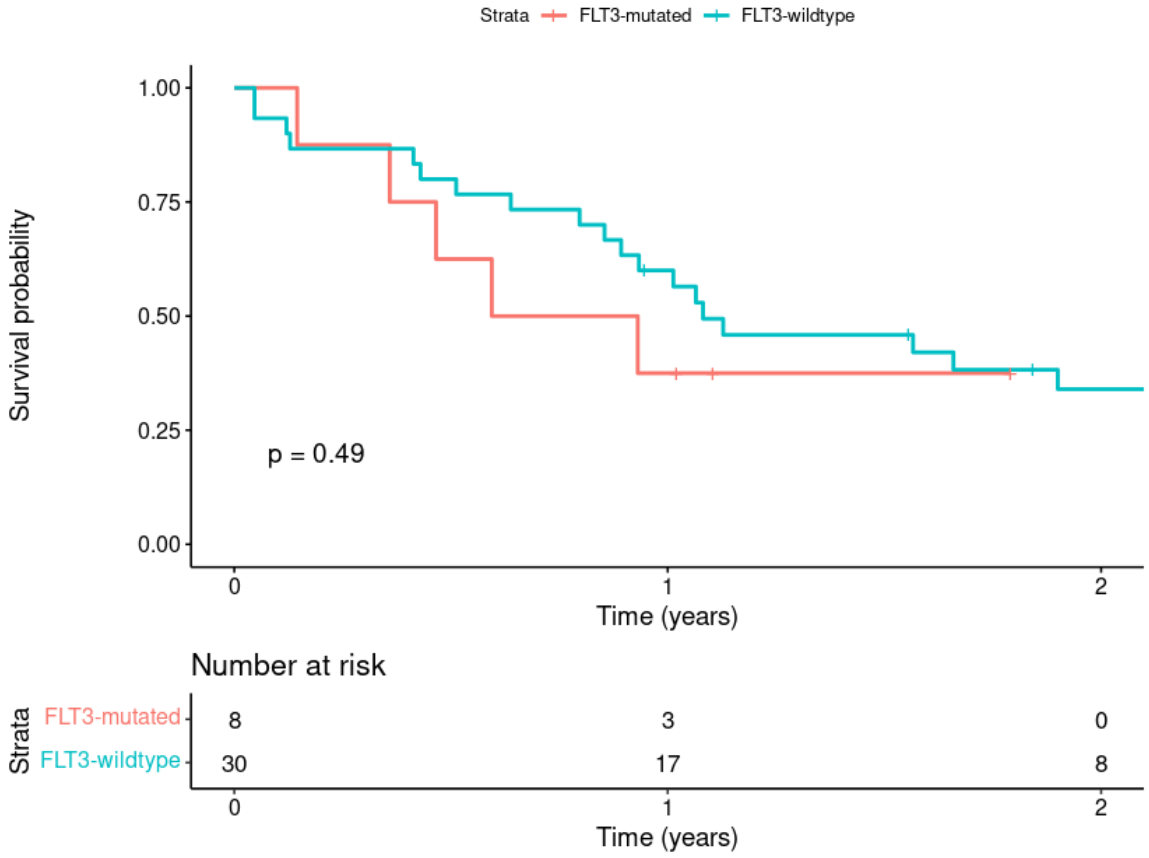
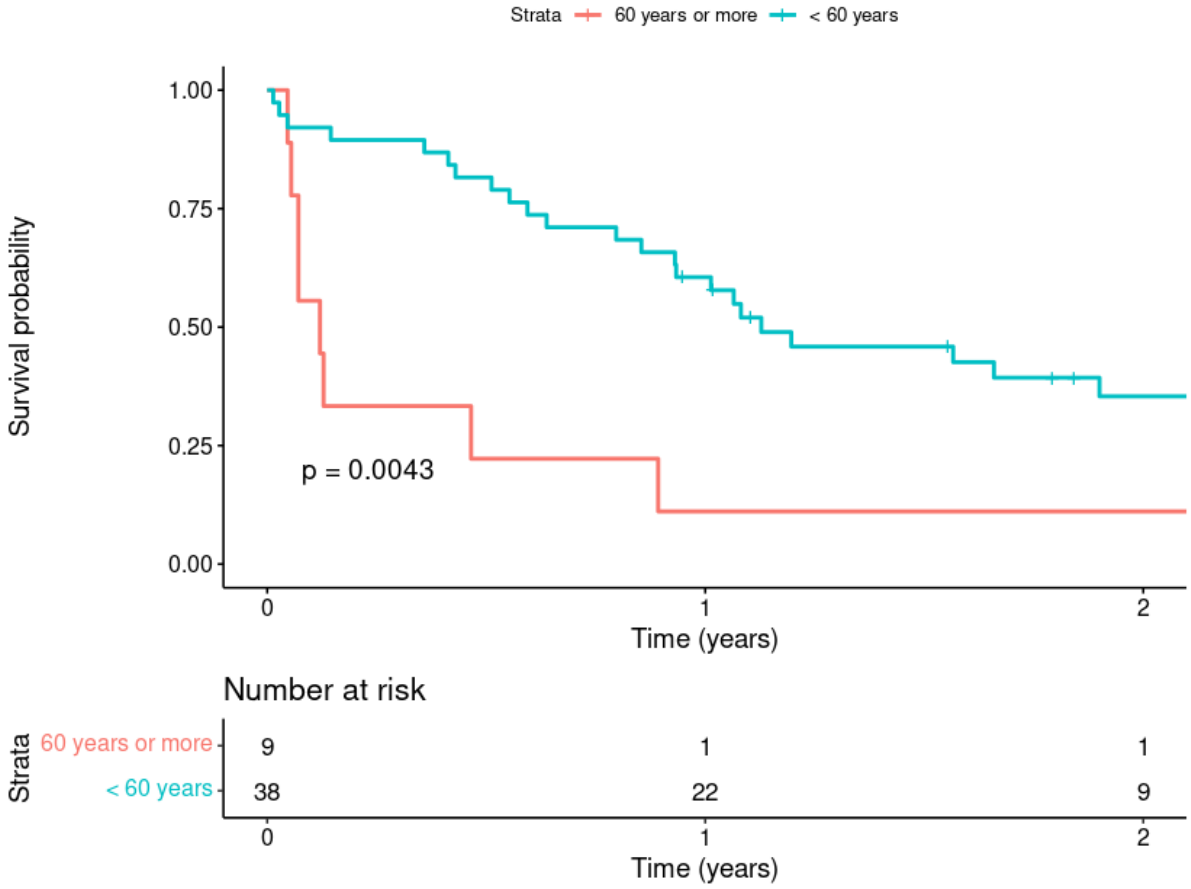


FIGURE 4: Overall survival by age group



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