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Original Article

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Survival in Elderly Patients Diagnosed With Acute Myeloid Leukemia: A Hospital-Based Study

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Abstract

Background: Acute myeloid leukemia (AML) is a hematological neoplasm that is more frequent in elderly patients. The objective of this study was to evaluate elderly patients' survival with *de novo* AML and acute myeloid leukemia myelodysplasia-related (AML-MR), treated with intensive and less-intensive chemotherapy and supportive care.

Methods: A retrospective cohort study was conducted in Fundacion Valle del Lili (Cali, Colombia), between 2013 and 2019. We included patients ≥ 60 years old diagnosed with AML. The statistical analysis considered the leukemia type (*de novo* vs. myelodysplasia-related) and treatment (intensive chemotherapy regimen, less-intensive chemotherapy regimen, and without chemotherapy). Survival analysis was performed using Kaplan-Meier method and Cox regression models.

Results: A total of 53 patients were included (31 *de novo* and 22 AML-MR). Intensive chemotherapy regimens were more frequent in patients with *de novo* leukemia (54.8%), and 77.3% of patients with AML-MR received less-intensive regimens. Survival was higher in the chemotherapy group (P = 0.006), but with no difference between chemotherapy modalities. Additionally, patients without chemotherapy were 10 times more likely to die than those who received any regimen, independent of age, sex, Eastern Cooperative Oncology performance status, and Charlson comorbidity index (adjusted hazard ratio (HR) = 11.6, 95% confidence interval (CI) 3.47 - 38.8).

Conclusions: Elderly patients with AML had longer survival time when receiving chemotherapy, regardless of the type of regimen.

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Introduction

Acute myeloid leukemia (AML) is a hematological neoplasm characterized by the malignant clonal expansion of progenitor cells coupled with a differentiation arrest [1]. Although epidemiological behavior shows a higher frequency in people over 65 years old, this pathology can appear at any age. The Surveillance, Epidemiology, and End Results (SEER) program estimated that in 2020, approximately 19,940 new cases would be diagnosed with about 11,180 deaths in the United States alone [2, 3]. Historically, elder age groups have represented a challenge in cancer treatment [4]. A lower tolerance and treatment response is conditioned by a decreased functional-state and age-related morbidities, as well as history of hematologic disorders, such as myelodysplastic syndrome and tumor biology [5]. Moreover, as population continues to age, the number of new AML cases increases by approximately 2.2% each year, representing a challenge for decision-makers [6].

The population-based cancer registry in Cali estimated myeloid leukemia's age-standardized incidence rate (ASIR) per 100,000 person-years was 3.1 for men and 2.1 for women between 2013 and 2017 [7]. In specified leukemias, the ASIR was 12.8 between 60 and 64 years of age and 48 between 75 and 79 years of age for men, while the ASIR was 8.2 and 27.5 for women, in the same age group between 2013 and 2017 [8]. The data suggest clinical differences by age that determine the AML's behavior even between elderly patients. For that reason, elderly patients are a unique and heterogeneous group. The therapeutic approach and intention to treat depend on a comprehensive evaluation of the patients; however, this population's best approach remains controversial [5, 9].

Current literature supports the necessity of an individualized approach to make treatment decisions beyond chronological age alone [10, 11]. This observational study evaluated elderly patients' survival with *de novo* and acute myeloid leukemia with myelodysplasia-related changes (AML-MRC), now called AML myelodysplasia-related (AML-MR), treated in routine clinical practice with intensive chemotherapy, less-

intensive chemotherapy, and supportive care in a single-center located in Cali, Colombia.

Materials and Methods

Study design and patient selection

A single-center retrospective cohort study was conducted at Fundacion Valle del Lili (Cali, Colombia) between 2013 and 2019.

Patients ≥ 60 years old with diagnosed AML were included. The exclusion criteria were patients with acute promyelocytic leukemia, megakaryoblastic leukemia, and incomplete clinical records. To obtain cases, the Department of Data Management tallied the International Classification of Diseases, 10th Revision (ICD-10) codes related to AML in our databases and then, we obtained the clinical data through revision of the clinical records.

Baseline and clinical characteristics

Sociodemographic and clinical variables were described according to the type of AML diagnosed, whether *de novo* or AML-MR.

AML-MR was defined as a neoplasm with ≥ 20% blasts expressing a myeloid immunophenotype and harboring specific cytogenetic and molecular abnormalities associated with myelodysplastic neoplasms (MDS), arising *de novo* or following a known history of MDS or MDS/myeloproliferative neoplasms (MPN) [12].

Prophylaxis was defined according to the institutional protocol that includes management with acyclovir 400 mg every 12 h and posaconazole 300 mg every 12 h on day 1, followed by 300 mg daily. Patients do not receive antibiotic prophylaxis according to this protocol.

Patients were classified in two groups considering the chemotherapeutic scheme: 1) intensive chemotherapy regime: cytarabine and anthracyclines (7 × 3); 2) less-intensive chemotherapy regime: cytarabine and anthracyclines (5 × 2), fludarabine and cytarabine, azacitidine or methotrexate associated with 6-mercaptopurine. Palliative care treatment included pain and symptom control plus family support. The type of treatment was defined by a multidisciplinary group, where hematologists, geriatrics and palliative care physicians participated.

Eastern Cooperative Oncology Group (ECOG) performance status was obtained to determine patient's aptness to tolerate therapies (0: asymptomatic; 1: symptomatic but completely ambulatory; 2: symptomatic, < 50% in bed during the day; 3: symptomatic, > 50% in bed, but not bedbound; 4: bedbound; 5: death) [13, 14]. Charlson comorbidity index (CCI) was estimated to predict 10-year survival in patients with multiple comorbidities [15, 16].

Measurable residual disease (MRD) was defined as the presence of leukemia cells down to levels of $1:10^4$ to $1:10^6$ white blood cells (WBCs), compared with 1:20 in morphology-based assessments [17]. It was determined using Navios EX™ flow cytometry (CE-IVD; 3 lasers, 10 colors; Beckman Coulter, Inc., USA) for immunophenotypic markers (CD15, CD117, CD33, CD13, human leukocyte antigen (HLA)-DR, CD34, CD16, CD11b, CD19, CD45, CD36, CD64, CD7, IREM, CD56, CD14, CD33) together with parameters of size and internal complexity (Forward Scatter/Side Scatter, FSC/SSC). The leukemia-associated immunophenotypes (LAIP) approach was implemented, which defines LAIPs at diagnosis and tracks these in subsequent samples.

Study outcomes

The primary outcome was the overall survival (OS). The time interval for survival analysis was from the date of diagnosis to the date of death or last follow-up (last day attended in the hospital), considering the chemotherapy regimen used and AML type.

Statistical analysis

Categorical variables were summarized in absolute and relative frequency tables, comparing them with χ^2 or Fisher's exact test. Quantitative variables were described with median (Me) and interquartile range (IQR), as they all had skewed distribution and were compared using Mann-Whitney's U test. The bivariate analysis compared the chemotherapy regimen and some clinical characteristics using crude odds ratio (OR) to determine possible associations between variables. Survival was analyzed through confuser-adjusted Kaplan Meier functions, comparing them with the log-rank and Wilcoxon tests. A Cox regression was performed to model the hazard ratio (HR) considering variables of clinical or statistical importance. The Cox regression's proportional risk assumption was verified by analyzing the Schoenfeld residuals and using goodness-of-fit graphical methods. A P value < 0.05 was considered significant for all statistical analyses. All analyzes used Stata® (Version 14.0, StataCorp LP, College Station, TX).

Ethics approval

The Institutional Review Board (Comite de Etica en Investigacion Biomedica of Fundacion Valle del Lili) approved this study (IRB/EC No. 1447); it followed the ethical principles for medical research outlined by the Declaration of Helsinki and considered the regulations of Resolution 8430/1993 of the Ministry of Health of Colombia.

Results

A total of 53 AML cases were included in the study; of these, 31 were *de novo* and 22 were AML-MR (Fig. 1).

Sociodemographic and clinical characteristics, according to the AML type, are shown in Table 1. The median age was 71 years (IQR: 67 - 77 years), with similar sex distribu-

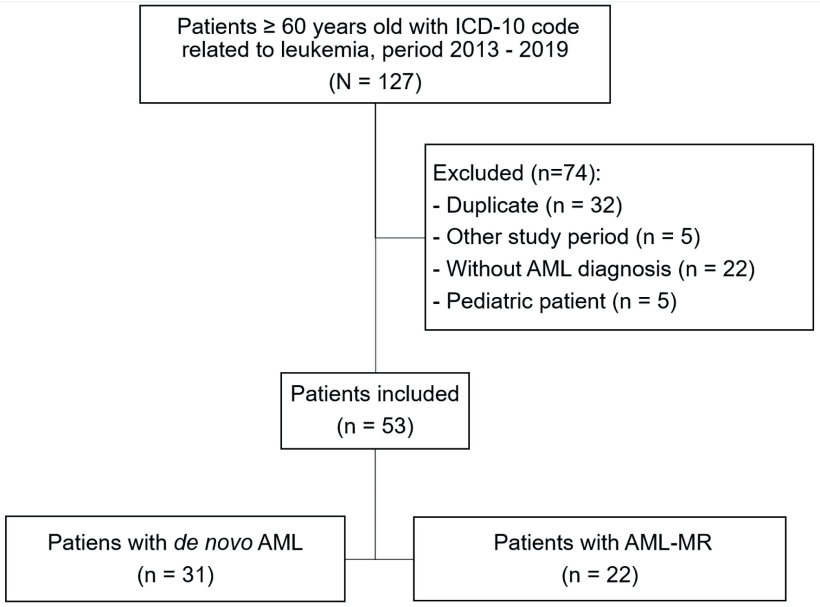

Figure 1. Flowchart of patient selection in the study. ICD-10: the International Classification of Diseases, 10th Revision; AML: acute myeloid leukemia; AML-MR: acute myeloid leukemia myelodysplasia-related.

Table 1. Demographic and Clinical Characteristics of Patients Included in the Study (N = 53)

Characteristic	Type of leukemia		P value
	De novo, n (%) (n = 31)	AML-MR, n (%) (n = 22)	
Median age at diagnosis (IQR) (years)	70 (66 - 77)	73 (68 - 78)	0.270
Female sex	16 (51.6%)	10 (45.5%)	0.659
Extramedullary involvement	5 (16.1%)	1 (4.5%)	0.195
Median white blood count (IQR) (/µL)	12,010 (2,100 - 45,530)	3,995 (1,070 - 12,490)	0.080
ECOG performance status			
1	20 (64.5%)	12 (54.5%)	0.070
2	1 (3.2%)	6 (27.3%)	
3	6 (19.4%)	3 (13.6%)	
4	4 (12.9%)	1 (4.5%)	
Charlson comorbidity index (CCI)			
4	8 (25.8%)	3 (13.6%)	0.282
≥ 5	23 (74.2%)	19 (86.4%)	
Drug therapy			
Intensive chemotherapy	17 (54.8%)	3 (13.6%)	0.001
Less-intensive chemotherapy	9 (29.0%)	17 (77.3%)	
No chemotherapy	5 (16.1%)	2 (9.1%)	
Support treatments			
Erythropoietin	1 (3.2%)	8 (36.4%)	0.002
Blood component transfusion	16 (51.6%)	18 (81.8%)	0.024
Palliative care	17 (54.8%)	11 (50.0%)	0.728
ICU management	25 (80.6%)	17 (77.3%)	0.513
Median survival (IQR) (days)	222 (28 - 659)	200 (54 - 360)	0.801

AML-MR: acute myeloid leukemia myelodysplasia-related; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range.

Table 2. Factors Related to the Chemotherapy Scheme

Characteristic	Chemotherapy scheme		OR (95% CI)	P value
	Intensive, n (%), (n = 20)	Less-intensive, n (%), (n = 26)		
Type of leukemia				
De novo	17 (85%)	9 (34.6%)	1	< 0.001
Myelodysplasia-related	3 (15%)	17 (65.4%)	0.9 (0.014 - 0.47)	
ECOG performance status				
1	19 (95%)	12 (46.2%)	1	< 0.001
≥ 2	1 (5%)	14 (53.8%)	0.05 (0.001 - 0.39)	
Charlson comorbidity index (CCI)				
4	10 (50%)	1 (3.8%)	1	< 0.001
≥ 5	10 (50%)	25 (96.2%)	0.04 (0.0008 - 0.36)	
Minimum residual disease (MRD)[a]				0.276
Detected	8 (57.1%)	10 (76.9%)	0.4 (0.05 - 2.7)	
Not detected	6 (42.9%)	3 (23.1%)	1	
Salvage chemotherapy				0.086
Yes	12 (60%)	9 (34.6%)	2.8 (0.72 - 11.23)	
No	8 (40%)	17 (65.4%)	1	

[a]Data available (n = 27). ECOG: Eastern Cooperative Oncology; IQR: interquartile range; CI: confidence interval.

tion. Nearly 72% of patients were from urban areas. Patient's performance status showed that 60.3% of them had an ECOG performance status of 1. Almost 80% had a CCI greater than 5. Chemotherapy with the intensive regimen was more common in patients with *de novo* AML (54.8%), while 77.3% of patients with AML-MR received less-intensive regimens. Thirteen percent of the patients did not receive any chemotherapy scheme. Most patients received blood transfusions as supportive management (64.2%, P = 0.004), but this procedure was more frequent in the AML-MR group (81.8%, P = 0.024), as well as the use of erythropoietin (36.4%, P = 0.002). Other clinical characteristics such as leukocyte count, extramedullary involvement, palliative care interventions, and intensive care unit (ICU) management did not have differences between AML types. The main complications during treatment according to the type of AML are shown here (Supplementary Material 1, www.thejh.org).

The median follow-up was 208 days (IQR: 36 - 454 days). The median survival between the two diagnostic groups was similar. About 74% of the entire cohort had died by the time follow-ups concluded.

Chemotherapy regimens

Table 2 describes chemotherapy regimens and their relation to some clinical features. Of 46 patients who received chemotherapy, 43.5% had an intensive regimen with cytarabine and anthracycline in a 7 × 3 scheme. While less-intensive regimens included cytarabine and anthracyclines in a 5 × 2 scheme (21.7%), fludarabine/cytarabine (13%), azacitidine (13%), or methotrexate and 6-mercaptopurine (8.7%).

Clinical factors associated with lower use of intensive chemotherapy regimen were a diagnosis of AML-MR (OR = 0.9, 95% CI: 0.014 - 0.47), an ECOG performance status over 2 (OR = 0.05, 95% CI: 0.001 - 0.39), and a CCI of 5 or higher (OR = 0.04, 95% CI: 0.0008 - 0.36). Other factors such as the use of salvage treatment and the presence of MRD were not related to the type of chemotherapy used.

Survival analysis

The median days of OS among patients treated with chemotherapy was higher than those who did not receive any regimen (250 days vs. 28 days, P = 0.001). However, there was no difference in survival time based on chemotherapy regimen administered (Table 3). Also, Kaplan Meier's function showed that at any time during follow-up, the adjusted survival probability was higher among the chemotherapy group vs. without chemotherapy (P = 0.006). There were no statistical differences in survival time, according to the chemotherapy regimen used (P = 0.938). However, the probability of surviving longer tends to be remarkable in the less-intensive chemotherapy group (Fig. 2). No differences in survival functions were found according to the type of AML (Supplementary Material 2, www.thejh.org).

The adjusted Cox regression model showed that at any time during follow-up, patients who did not receive chemotherapy were 10 times more likely to die compared to those who received chemotherapy, regardless of age, sex, ECOG performance status, and CCI (HR = 11.6, 95% CI: 3.47 - 38.8). The Cox model's Schoenfeld scale plot showed a horizontal line, and the rho test was not significant (P = 0.969). The Mar-

Table 3. Overall Survival by Chemotherapy Scheme

	Chemotherapy (n = 46)			No chemotherapy (n = 7)	P value
	Intensive	Less-intensive	P value		
Median overall survival (IQR), days[a]	266.5 (137.5 - 565.5)	223.5 (54 - 477)	0.658	28 (2 - 36)	0.001
Probability of survival, %[a]					
30 days	78.6	75.4	0.938	< 1	0.006
First year	25.0	38.6		-	
Second year	8.6	32.4		-	
Third year	-	24.2		-	

[a]Adjusted by ECOG performance status, Charlson comorbidity index (CCI), and type of diagnosis. IQR: interquartile range; ECOG: Eastern Cooperative Oncology.

tingale residue plot and the survival curve represented with Nelson Aalen's method drew a 45-degree line. The proportionality criterion was satisfied.

Discussion

AML disproportionately affects elderly population. It represents a treatment challenge due to patients' decreased functional status and the neoplasm's more aggressive behavior in this age group. Developing a standardized treatment approach is complex, and the best therapeutic choice for this population remains controversial. It has been shown that the efficacy and tolerability of treatment deteriorates markedly with age [5, 18].

This study evaluated the treatment and survival of elderly patients with *de novo* and AML-MR. We found that patients who received chemotherapy had a significantly higher OS compared with patients with non-pharmacological intervention. However, survival analyzes of chemotherapy schemes did not evidence statistically significant differences between intensive or less-intensive therapy.

These results have been supported in previous studies that involved elderly patients. A phase 3 clinical trial showed that AML elderly patients who received intensive induction chemotherapy had improved survival at 2.5 years and higher remission rates than supportive care [19]. A retrospective study conducted in the USA analyzed, among Medicare beneficiaries, the treatment patterns and outcomes of elderly AML patients. It found a significant survival benefit between those who received antileukemic therapy (with intensive and less-intensive schemes) compared to support treatment [20]. These findings are consistent with the recommendation published by the National Cancer Comprehensive Network guidelines in their third version, which established that age alone should not be the sole factor in determining the treatment scheme chosen in AML patients [21]. Our results reported an adjusted chance of dying 10 times greater for patients who did not receive chemotherapy.

A phase 3, multicenter, randomized, double-blind, place-

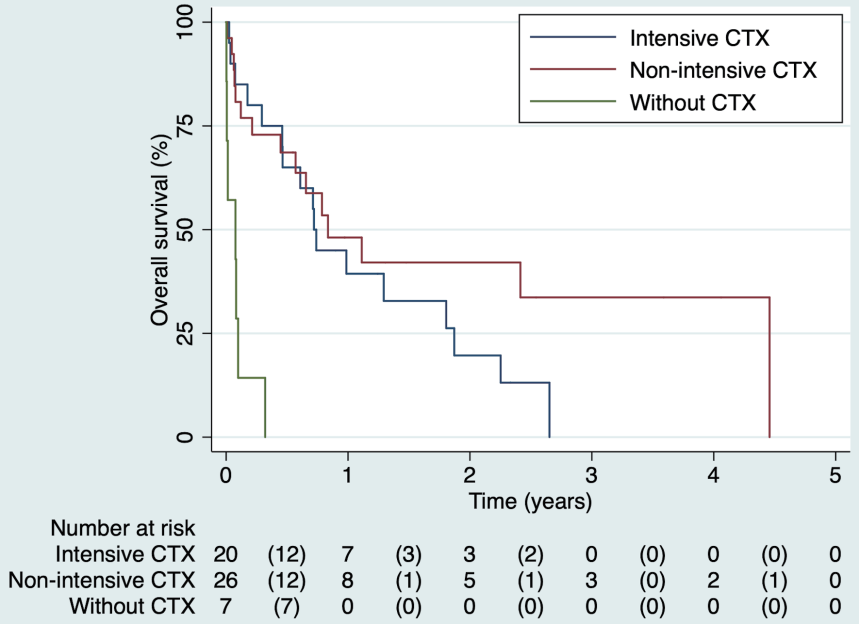

Figure 2. Kaplan's survival function by chemotherapy scheme. CTX: chemotherapy.

bo-controlled trial evaluated azacitidine plus venetoclax vs. azacitidine plus placebo in untreated patients aged ≥ 75 years old who were ineligible for intensive chemotherapy. Their findings showed that patients who received azacitidine plus venetoclax OS was longer (median OS 14.7 months vs. 9.6 months; HR = 0.66, 95% CI: 0.52 - 0.85, P < 0.001) and the incidence of remission was higher (36.7% vs. 17.9%, P < 0.001), but with a higher incidence of febrile neutropenia (42% vs. 19%) [22]. However, the use of venetoclax has only recently been implemented in Latin America (since 2019 in some countries), that is why future studies are required to evaluate its efficacy in older patients with AML in the region.

Although there were no statistically significant differences between intensive and less-intensive chemotherapy regimens in this study, data suggest a higher survival trend among patients who received less-intensive modalities. Nonetheless, a longer follow-up and sample size would be required to verify this finding. Quintas-Cardama et al showed that survival in patients treated with less-intensive therapy was non-inferior to that achieved with intensive chemotherapy. The study states that despite hypomethylating therapy resulting in lower complete remission rates, it may result in leukemia control and mortality reduction, particularly in AML elderly patients with adverse cytogenetic presentations [23]. Meanwhile, Dombret et al found improvement in OS in the less-intensive group compared with conventional care. It also reported low complete response rate but a survival benefit between the participants [24]. These findings could explain that less-intensive schemes are better tolerated by elderly patients [25].

Whereas there is some evidence to suggest that less-intensive chemotherapy is the best option in AML elderly patients, other studies favor intensive schemes. Bell et al compared intensive induction chemotherapy vs. treatment with hypomethylating agents in AML elderly patients [26]. They demonstrated that the median OS was significantly higher in patients treated with intensive regimens even when it is well known that hypomethylating agents are usually selected for elderly patients that tend to have more comorbidities [20].

Despite these results, many elderly patients had considerable morbidity and mortality from intensive chemotherapy, increasing significantly with age, and decreased performance status [27]. A retrospective analysis of elderly patients receiving intensive chemotherapy at MD Anderson Cancer Center demonstrated a 28-day mortality risk higher between comorbid patients than healthy ones. Patients with a score ≥ 3 on the Hematopoietic Stem Cell Transplant comorbidity index had a 29% chance of 28-day mortality risk compared with 11% for patients with lower scores [28]. Likewise, Appelbaum et al reported a 30-day mortality risk for patients with ECOG performance status of 2, as 31%, in 66 to 75 years old patients [29]. The previous results suggest that the cornerstone to decide the treatment option in an elderly leukemia patient is to determine their functional state because it determines which treatment goal to pursue [30, 31]. Therefore, looking beyond OS as the primary endpoint may be appropriate in elderly patients with AML. Also, considering the disease-related quality of life as a suitable endpoint, mostly because they rarely achieve a cure [32].

A comprehensive geriatric assessment as a standard of evaluation between elderly patients should be mandatory [9, 33]. This approach classifies patients as fit, vulnerable, or frail predicting the therapy response and adverse effects likelihood [11, 34]. Although these tools have been validated for AML patients, their use is not widespread in clinical practice. This study found that our patients' functional status was evaluated through the ECOG performance status and CCI. In our context, the hematologists did not use a comprehensive geriatric assessment as literature recommends, but we had the support of a multidisciplinary group.

Another finding of our study was that AML-MR patients had a lower probability of receiving an intensive chemotherapy regime compared with *de novo* AML patients (13.6% and 54.8%, respectively, P = 0,003). Considering our results, the subtype of AML determined the curative intention. Other studies also reported the preference for less-intensive therapies in this group [35, 36], which could be explained by a decrease at complete remission rates, OS, and worse prognosis observed among these patients [37]. Other factors, such as age, comorbidities, lower functional status, and cytotoxic treatment history, also condition the therapeutic election [38]. In fact, a study reported in 2014 that prior treatment with hypomethylating agents could induce tumoral cells and immunological changes that will result in resistance to the same pharmacological class in the future [39].

When comparing the *de novo* and AML-MR patients, the literature reports among the second group a trend of older age, comorbidities, low-risk cytogenetics, and worse ECOG performance status [36, 40]. Identified factors that have an impact in AML-MR are the presence of mutations in specific cellular populations that may define secondary nature and adverse outcomes of AML (*ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1* and *ZRSR2*), presence of MDS-defining cytogenetic abnormalities, or disease secondary to a previously treated myeloid malignancy (treated-secondary AML, ts-AML), cytogenetic abnormalities that include complex karyotype-3 or more abnormalities balanced translocations and unbalanced translocations, degree of differentiation, myeloid lineage involved, and dysplastic changes [38, 41, 42].

Our results do not show differences between these populations. This could be explained because both groups were similar in age, gender, ECOG performance status, and CCI; as well as the exposure of hypomethylating agents in both groups and the frequency of complications during treatment. Finally, the low number of patients could be explained by the fact that the study was conducted in only one center. Therefore, we recommend exploring the *de novo* AML and AML-MR Colombian population in future prospective studies with a larger sample size and exploring associated biological and genetic factors.

Limitations

The results of this study should be interpreted in the context of a retrospective cohort. First, it was conducted retrospectively at a single center, limiting the sample size and implying selection and information biases. Secondly, it was not possible to describe chemotherapy response because post-chemotherapy myelogram data were not available in most clinical records. It is an important parameter to consider in the treatment of AML

patients, so it should be included in future studies. Third, the heterogeneity of less-intensive schemes administered to the patients' limits developing a pharmacological specific analysis because low number of patients on each treatment. Although less-intensive chemotherapy schemes often include cytarabine plus anthracyclines in a 5 + 2 regimen, this therapy was used in vulnerable patients (those dependent on instrumental activities of daily living (IADL) and with some comorbidity), while the 7 + 3 scheme was used in fit patients (independent patients in basic activities of daily living (BADL) and IADL, and without associated comorbidity) [43]. Regarding the use of venetoclax, the National Institute for Food and Drug Surveillance (INVIMA) approved its use in Colombia in 2020, but for AML treatment it was authorized in 2021, so the patients included in the study could not receive it. In addition, the approval by the regulatory body does not imply that the patient would have had access to the drug since that also depends on aspects related to the healthcare system (i.e., access to the health system, drug supply management, financing, coverage, among others). Fourth, the lack of a geriatric assessment model used at patients' functional status evaluation revealed the necessity of hematologists and palliativist having familiarity with these tools. Specially because these instruments are validated for AML patients, and evidence favors them over others predicting mortality and chemotherapy toxicity. Finally, due to the dynamic cohort, patients admitted in the last year of the study (2019) had shorter follow-up times. To mitigate bias, we adjusted the analyzes for the cohort effect.

Despite the limitations, these findings contribute to the better knowledge and characterization of AML in the elderly population because we described the treatment patterns and survival in our context. Besides, we included *de novo* and AML-MR, which allowed us to independently analyze the effect of treatment in both types of AML, thus being one of the few studies that include patients with both diagnoses. This is useful for the medical community that handles patients with similar characteristics.

Conclusions

Elderly AML patients (over 60 years old) had a significant survival benefit with chemotherapy intervention compared with supportive care or non-pharmacological treatment. However, it was nonrandomized and retrospective and based on experience with a small patient population at one center.

Supplementary Material

Suppl 1. Main complications during treatment according to the type of AML.

Suppl 2. Kaplan's survival function by type of AML.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that they have no competing interests.

Informed Consent

As this is a retrospective study, patient informed consent was not required.

Author Contributions

DM Mendoza-Urbano and E. Arrieta participated at conceptualization; J. Rosales and FE Ahumada planned the methodology; DM Mendoza-Urbano and ME Tello-Cajiao did the validation; ME Tello-Cajiao and LG Parra- Lara performed the formal analysis; DM Mendoza-Urbano and ME Tello-Cajiao prepared the original draft; LG Parra- Lara and FE Ahumada reviewed and edited the first draft; J. Rosales performed the project supervision. All authors made significant contributions to writing the manuscript, read and approved the final manuscript.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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