Treatment patterns and clinical outcomes in acute myeloid leukemia patients who are not eligible for intensive induction chemotherapy: A real-world study from Latin-America

Patrones de tratamiento y resultados clínicos en pacientes con leucemia mieloide aguda no elegibles para quimioterapia de inducción intensiva: estudio de vida real en América Latina

Kenny Mauricio Gálvez-Cárdenas[1], Leonardo José Enciso-Olivera[2], César Augusto Samanez-Figari[3], Shirley Quintana-Truyenque[4], Benito Arturo Castillo-Ríos[5], Guillermo Enrique Quintero-Vega[6], Elizabeth Arrieta-López[7], Alexis Javier Pinto-Gómez[8], Sandra Aruachan-Vesga[9], María Isabel Durán-Sánchez[10], Germán Espino-Lopéz[11]

Abstract. Introduction. *There is a knowledge gap concerning patients with acute myeloid leukemia (AML) who are not eligible for intensive induction chemotherapy; this, together with a recent increase in the incidence in Latin America, encloses a need. Through real-world evidence, we describe and compare the results of the different treatment strategies within this context.* ***Methodology.*** *This is a longitudinal, descriptive, retrospective study of a cohort of Latin American patients with AML not eligible for intensive induction chemotherapy, treated with low-intensity chemotherapy or with the best supportive care alone between January 1, 2015, to December 31, 2018.* ***Results.*** *Of a total of 125 patients (median age 74.8 years), the majority received low-intensity chemotherapy (78.4%). The median time in months of overall survival (9.2), progression-free survival (4.8), and time to treatment failure*

[1] Médico, Especialista en Medicina Interna, Especialista en Hematología, Hospital Pablo Tobón Uribe. Medellín, Colombia. E-mail: kennygalvez@gmail.com.
[2] Médico, Especialista en Hematología, Instituto Nacional de Cancerología. Bogotá, Colombia.
[3] Médico, Especialista en Hematología, AUNA-Oncosalud. Lima, Perú.
[4] Médica, Especialista en Oncología, Instituto Nacional de Enfermedades Neoplásicas, INEN. Lima, Perú.
[5] Médico, Especialista en Hematología, Departamento Oncológico, Instituto Oncológico de Panamá. Ciudad de Panamá, Panamá.
[6] Médico, Especialista en Hematología, Fundación Santa Fe de Bogotá. Bogotá, Colombia.
[7] Médica, Especialista en Hematología, Departamento de Hematología, Fundación Valle del Lili. Cali, Colombia.
[8] Médico, Especialista en Hematología, Servicio de Hematología, Complejo Hospitalario Dr. Arnulfo Arias Madrid (CH-DrAAM), Centro Oncológico de Panamá (COPSA), Hospital Santa Fe. Ciudad de Panamá, Panamá.
[9] Médica, Clínica IMAT Oncomédica. Montería, Colombia.
[10] Médica, Especialista en Epidemiología, MSc en Ciencias Biológicas, AbbVie S.A.S. Bogotá, Colombia.
[11] Médico, Especialista en Hematología, Centro Hemato-Oncológico Panamá (CHOP). Ciudad de Panamá, Panamá.

Declaration of interest: The design, study conduction, and financial support for the study were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication. IQVIA has served as consultants to AbbVie and has received research financial support from AbbVie. AbbVie provided funding to IQVIA for this work. No honoraria or payments were made for authorship.
Medicina & Laboratorio 2023;27:315-332. https://doi.org/10.36384/01232576.683.
Recibido el 27 de abril de 2023; aceptado el 4 de julio de 2023. Editora Médica Colombiana S.A., 2023©.

(3.8) were longer in patients receiving hypomethylating agents. Additionally, better results were observed with low-intensity chemotherapy (complete response 11.2% and stable disease 17.3%) compared to the best supportive care alone. ***Conclusion.*** *We deliver a real-world standpoint of Latin American patients with AML who are not eligible for intensive induction chemotherapy. Our findings pave the first steps of the way to describe, understand, and support informed decision-making processes in our region.*

Keywords: *acute myeloid leukemia, real-world, treatment outcome, antimetabolites, antineoplastic, Latin America.*

Resumen. Introducción. *Existe una brecha en el conocimiento de los pacientes con leucemia mieloide aguda (LMA) no elegibles para quimioterapia intensiva de inducción; que, en conjunto con un aumento reciente de su incidencia en Latinoamérica, condiciona una necesidad. A través de evidencia del mundo real, se describen y se comparan los resultados de las diferentes estrategias de tratamiento bajo este contexto.* ***Metodología.*** *Se presenta un estudio longitudinal, descriptivo, retrospectivo de una cohorte de pacientes latinoamericanos con LMA no elegibles para quimioterapia de inducción intensiva, tratados con quimioterapia de baja intensidad o con el mejor cuidado de soporte únicamente, entre el 1 de enero de 2015 y el 31 de diciembre de 2018.* ***Resultados.*** *De un total de 125 pacientes (edad media 74,8 años), la mayoría recibió quimioterapia de baja intensidad (78,4 %). La mediana en meses de supervivencia general (9,2), de supervivencia libre de progresión (4,8) y del tiempo hasta el fracaso del tratamiento (3,8) fueron mayores en pacientes que recibieron agentes hipometilantes. Adicionalmente, se observaron mejores resultados con la quimioterapia de baja intensidad (respuesta completa en 11,2 % y enfermedad estable en 17,3 %) frente al mejor cuidado de soporte únicamente.* ***Conclusión.*** *Exponemos una visión del mundo real de los pacientes latinoamericanos con LMA que no son elegibles para quimioterapia de inducción intensiva. Nuestros hallazgos son un primer paso en el camino para describir, comprender y respaldar los procesos informados de toma de decisiones en nuestra región.*

Palabras clave: *leucemia mieloide aguda, evidencia del mundo real, tratamiento, antimetabolitos, antineoplásicos, América Latina.*

Introduction

Acute myeloid leukemia (AML) is a heterogeneous, clonal hematologic malignancy involving the infiltration of immature myeloid cells into the bone marrow, peripheral blood, and other tissues [1]. AML is common in older people, with a median age of diagnosis in developed countries of 68 years [2]. Overall, AML accounted for 23% of all leukemia cases worldwide in 2017, with $119.57x10^3$ incident cases and $99.90x10^3$ related deaths [3,4]. The age-standardized incidence rate of AML increased from 1.35/100,000 in 1990 to 1.54/100,000 in 2017 globally, with the fastest rise observed in Andean Latin America of up to 1.40/100,000 in 2017, corresponding to an estimated annual percentage

change for 1990-2017 of 1.68 (95% CI 1.55-1.82) [3,4] and the incidence is projected to increase with the rise in the global aging population [5].

Regarding the global burden of the disease, AML is deemed as costly. First of all, considering its effects from a social perspective on the patients' functionality, quality of life, and productivity, there has been estimated a significant morbidity burden increase of 56.14% from 2,063,000 disability-adjusted life years (DALYs) in 1990 to 3,221,000 in 2017 [6]. Secondly, from a healthcare system or payer perspective, the highest expenses are owed to the treatment (i.e., chemotherapy and hematopoietic stem cell transplant); additional direct medical costs include outpatient care, physician visits, hospitalization, palliative care, complications prophylaxis, and monitoring [7,8]. The global burden of the disease ranges from 100-1,000 in Colombia, Peru, Ecuador, Venezuela, and Argentina and up to 1,000-10,000 in Brazil. Further, a significant increase in the 1990-2017 age-standardized DALY rate (EAPC=1.59, 95% CI 1.46-1.73) has been described for Andean Latin America [4].

Even though current progress in the understanding of the disease has enabled the introduction of medications with novel mechanisms of action, AML treatment continues to be challenging. Based on medical fitness and comorbid illnesses, patients eligible for intensive induction chemotherapy begin intravenous anthracycline treatment on days 1 to 3 (45-60 mg/m^2/day), along with a seven-day continuous infusion of cytarabine (100-200 mg/m^2/day) as the standard of care. After complete remission, consolidation therapy with one or more courses of chemotherapy (usually high-dose cytarabine) is recommended [9].

Nevertheless, some patients, particularly those >60 years of age, are usually considered "not eligible" for the aforementioned intensive induction therapy based on the fact that they are more likely to have unfavorable prognostic characteristics, poor functional status, multimorbidity, lower tolerability to the medication and even deleterious socioeconomic factors [10,11]; thus, conditioning poor outcomes with median survival ranging from 5 to 10 months [1]. Unfortunately, there is not a globally acknowledged standard of care for those not eligible patients [12]. Based on a risk-benefit balance, there are options, such as low-intensity chemotherapy (LIC), including a hypomethylating agent-based treatment (HMA) such as 5-azacitidine and decitabine or low-dose cytarabine (LDCA) for those who are not suitable for HMA-based treatment. Additionally, the best supportive care (BSC) (pain relief, nutritional support, infection management, hydroxyurea for cytoreduction, and/or transfusion support) alone is an alternative for more frail patients [9,13]. On the other hand, the current advent of novel therapies, such as B-cell lymphoma 2 (BCL-2) inhibitors (e.g., venetoclax), isocitrate dehydrogenase inhibitors, and monoclonal antibody therapy, have expanded the therapeutic landscape beyond BSC and LIC [14-16].

In Latin America, the context of the disease is utterly singular. The differential behavior of AML is conditioned by factors both inherent to the patient, such as the fact that in developing countries (e.g., Mexico or Brazil), the mean age at diagnosis has been estimated to be ten years earlier; as well as sociocultural aspects [17-19]. Barriers to therapy access play a pivotal role due to the limited health resources and the authorities' preference of allocating budget to more frequent cancers, looking for

a broader social impact rather than investing in such a costly disease [19,20].

Taken together, this context and the scarcity of evidence for this subpopulation in our region make evident the need to shorten the knowledge gap concerning the differences in the clinical course and therapy response of Latin American AML patients who are not eligible for intensive induction chemotherapy [11,21,22]. Accordingly, by assessing real-world data for this subpopulation, we aim to compare the overall survival (OS) for the different identified treatment strategies and to describe the clinical and paraclinical characteristics (pathological, cytogenetic, and molecular profiles) and the healthcare resource utilization (HCRU).

Methodology

We conducted a longitudinal, descriptive, retrospective study of a cohort of patients aged ≥18 years, diagnosed with either primary or secondary AML, who were not eligible for intensive induction chemotherapy based on the physician's assessment of age, ECOG performance status, comorbidities, regional guidelines, or institutional practice, or all these; as proposed by DiNardo et al. [23], between January 2015 and December 2018. In addition, all patients had to have received as a first-line treatment either systemic therapy including LIC (azacytidine/decitabine or LDCA), targeted therapy (gemtuzumab ozogamicin, enasidenib, FLT3 inhibitors, venetoclax or ivosidenib), or BSC (hydroxyurea or transfusion support). Patients with unconfirmed AML or acute promyelocytic leukemia diagnosis and those receiving first-line AML treatment as part of an ongoing clinical trial were excluded.

Data was extracted in an anonymized manner from patient charts across 10 community/hospital-based medical centers in Colombia (n=5), Panama (n=3), and Peru (n=2). Patients were followed up until the last recorded contact or death, whichever occurred first at time of data collection. In compliance with the local regulations, due to the anonymized nature of the data and the observational-descriptive nature of the study, after approval of the corresponding Ethics Committee no individual additional informed consent was obtained.

Baseline information included age at diagnosis, sex, the 2017 World Health Organization (WHO) classification system, the French-American-British (FAB) classification/morphologic subtype, the Eastern Cooperative Oncology Group (ECOG) performance status scores, comorbidities, bone marrow (BM) aspirate examination/biopsy, and immunophenotyping if available. Information on treatment patterns assessed during follow-up visits consisted of its type (LIC [LDCA or HMA] or BSC only), drugs, and reason for discontinuation (if applicable).

The main outcome was OS, defined as the time in months from the date of confirmed diagnosis of AML (i.e., the index date) to death from any cause. Other outcomes included: Progression Free Survival (PFS) measured from the date of confirmed diagnosis of AML to the date of physician-assessed disease progression or death due to any cause; Time to Treatment Failure (TTF) defined as discontinuation of treatment due to disease progression, death, decline in performance status, toxicity, and patient or physician choice; and response rate per physician assessment: Rates of Complete Remission (CR), CR with incomplete hematologic recovery (CRi), Partial Remission (PR), Stable Disease

(StD), Progressive Disease (PD), time to achieve the best response (any of the aforementioned), and treatment failure. HCRU was handled as the number of transfusions, the number, duration, and complexity of hospitalizations (ICU or general), and the number of outpatient consultations.

All statistical analyses were performed using the SAS software (SAS Institute Inc., Cary, NC). Continuous variables were described by the mean, standard deviation (SD), median, quartiles, and ranges according to their distribution. Categorical variables were reported as absolute and relative frequencies. After stratification by type of treatment, for survival/time to event analysis, proportions and median survival times were calculated through the Kaplan-Meier method.

Results

Baseline characteristics and follow-up

A total of 125 patients were included in the analysis. As shown in **table 1**, most patients were from Peru and Colombia; the minimum age was higher for patients receiving BSC only. The absence of comorbidities was more frequent for patients receiving LIC rather than BSC only (28 vs. 1); cardiovascular comorbidities were more frequent in the latter. The most common AML WHO category was AML not otherwise specified for both treatments; meanwhile, for BSC only, AML with myelodysplasia-related changes was less frequent. Additionally, according to the FAB classification, M2 and M4 were the most frequent subtypes. Detailed information on FAB classification, immunophenotyping, BM aspirate/biopsy examination, and comparative information per study site is presented in detail in **tables 2** and **3**. Because the number of patients in the study cohort from Panama was small, the findings for these patients are not discussed separately.

For 27 patients with secondary AML, the most common subtype was myelodysplastic syndromes (MDS) (n=15, 55.6%), and only 2 of them received prior HMA-based treatment for the antecedent disorder. Other secondary AML subtypes were chronic myelomonocytic leukemia (n=3, 11.1%), myeloproliferative neoplasms (n=2, 7.4%), and therapy-related AML (n=4, 14.8%); information was not available for 3 cases.

Regarding treatment patterns, as the first line of treatment, over half of those under the LIC regime received 5-azacitidine (n=54, 55.1%), followed by decitabine (n=5, 5.1%), LDCA (n=10, 10.2%) and other medications alone or in combination (n=34, 34.7%) such as cytarabine, aclarubicin, CAG regimen (low-dose cytarabine, aclarubicin hydrochloride and granulocyte colony-stimulating factor), enocitabine or venetoclax. Only four patients were treated with a combination therapy (LDCA+5-azacitidine or LDCA/5-azacitidine + other treatments). On the other hand, BSC consisted of transfusion support (n=13, 48.1%), pain relief (n=8, 29.6%), nutritional support (n=2, 7.4%), infection management (n=11, 40.7%), and other combinations including hydroxyurea (n=11, 40.7%). The mean time from diagnosis to initiation of treatment was 7.9 (SD 11.4) days.

Twenty-three patients required a second line of treatment with BSC (n=12, 52.2%) or LIC (n=11, 47.8%). Just less than half of those with LIC received 5-azacitidine (n=4, 36.4%), followed by decitabine (n=1, 9.1%), LDCA (n=4, 36.4%), venetoclax (n=1, 9.1%) and other medications (n=2, 18.2%). For

Tabla 1. Baseline clinical characteristics per type of first-line treatment

	LIC n=98 (78.4%)	BSC only n=27 (21.6%)	Total n=125
Sex, n (%)			
Male	54 (55.1)	13 (48.1)	67 (54)
Age at diagnosis			
Mean (SD)	74.4 (8.1)	76.0 (8.3)	74.7 (8.1)
Min-Max	41-87	62-88	41-88
WHO classification, n (%)			
AML with recurrent genetic abnormalities	3 (3.1)	0	3 (2.4)
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM	1 (33.3)	0	1 (33.3)
AML with mutated NPM1	2 (66.7)	0	2 (66.7)
AML with myelodysplasia-related changes	27 (27.6)	4 (14.8)	31 (24.8)
AML not otherwise specified	30 (30.6)	9 (33.3)	39 (31.2)
AML with minimal differentiation	3 (10.0)	2 (22.2)	5 (12.8)
AML without maturation	4 (13.3)	1 (11.1)	5 (12.8)
AML with maturation	11 (36.7)	1 (11.1)	12 (30.8)
Acute myelomonocytic leukemia	10 (33.3)	3 (33.3)	13 (33.3)
Acute monoblastic/monocytic leukemia	1 (3.3)	1 (11.1)	2 (5.1)
Acute megakaryoblastic leukemia	0	1 (11.1)	1 (2.6)
Acute panmyelosis with myelofibrosis	1 (3.3)	0	1 (2.6)
Unknown	38 (38.7)	14 (51.9)	52 (41.6)
Cytogenetic and molecular profiles			
Cytogenetics			
Favorable risk	4 (4.1)	-	4 (3)
Intermediate risk	33 (33.7)	3 (11.1)	36 (29)
Poor risk	11 (11.2)	1 (3.7)	12 (10)
Unknown	50 (51.0)	23 (85.2)	73 (58)
Mutation*			
Any[a]	9 (9.2)	-	9 (7)
FLT3	2 (22.2)	-	2 (22.2)
$FLT3^{ITD}$ [a]	1 (11.1)	-	1 (11.1)
Unknown	1 (100)	-	1 (100)
NPM1	4 (44.4)	-	4 (44.4)
Other	3 (33.3)	-	3 (33.3)
Unknown	1 (11.1)	-	1 (11.1)
None	24 (24.5)	6 (22.2)	30 (24)
Unknown	65 (66.3)	21 (77.8)	86 (69)

Table 1. Continued			
ECOG performance status, n (%)			
0	6 (6.1)	5 (18.5)	11 (8.8)
1	30 (30.6)	1 (3.7)	31 (24.8)
2	29 (29.6)	3 (11.1)	32 (25.6)
3	9 (9.2)	7 (25.9)	16 (12.8)
Unknown	24 (24.5)	11 (40.7)	35 (28)
Secondary AML, n (%)			
Yes	21 (21.4)	6 (22.2)	27 (21.6)
No	69 (70.4)	18 (66.7)	87 (69.6)
Unknown	8 (8.2)	3 (11.1)	11 (8.8)
Comorbidities*, n (%)			
Cardiovascular diseases	18 (18.4)	9 (33.3)	27 (21.6)
Elevated transaminases (not related to liver cirrhosis) or renal failure/CKD 3 or 4	8 (8.2)	1 (3.7)	9 (7.2)
Restrictive lung disease or COPD	3 (3.1)	2 (7.4)	5 (4)
Other	51 (52.0)	12 (44.4)	63 (50.4)
Primary location, n (%)			
Panama	10 (10.2)	6 (22.2)	16 (13)
Peru	47 (48.0)	12 (44.4)	59 (47)
Colombia	41 (41.8)	9 (33.3)	50 (40)[b]

AML: acute myeloid leukemia; BSC: best supportive care; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ECOG: Eastern Cooperative Oncology Group; LIC: low-intensity chemotherapy; SD: standard deviation; WHO: World Health Organization.
* Percentages may sum up to more than 100% as multi-selection was allowed. [a] Number used as denominator for the following sub-categories. [b] One patient received treatment in Colombia while the patient information was collected in other countries, outside of Latin America. Therefore, the patient data was excluded from the final analysis.

patients receiving BSC, the most common kind was transfusion support (n=8, 66.7%), followed by pain relief (n=6, 50%), infection management (n=3, 25%), and other combinations (n=4, 33.3%). The mean and median time from diagnosis to initiation of a second-line treatment was 159 (SD 198.45) and 90 (Min-Max 2-741) days, respectively.

Outcomes

At the end of follow-up (i.e., diagnosis to most recent record) for the LIC subgroup, 22 patients were alive and contributed a median follow-up time of 9.6 months (Min-Max 0.2-47.5); likewise, 67 patients died with a median time from diagnosis to death of 4.3 months (Min-Max 0.2-30.6), 9 patients were lost during follow-up. For the BSC-only subgroup, three patients were alive, with a median follow-up time of 0.9 months (Min-Max 0.3-2.6), and 22 were dead, with a median time from diagnosis to death of 1.3 months (Min-Max 0.1-9.5), 2 patients were lost during follow-up.

Median OS in months was the longest for patients treated with HMA thera-

Tabla 2. Type of AML and bone marrow aspirate at baseline

FAB, n (%)	**LIC n=98 (78.4%)**	**BSC only n=27 (21.6%)**
M0 Undifferentiated acute myeloblastic leukemia	11 (11.2)	3 (11.1)
M1 Acute myeloblastic leukemia with minimal maturation	11 (11.2)	2 (7.4)
M2 Acute myeloblastic leukemia with maturation	29 (29.6)	4 (14.8)
M4 Acute myelomonocytic leukemia	19 (19.4)	6 (22.2)
M5 Acute monocytic leukemia	8 (8.2)	1 (3.7)
M7 Acute megakaryoblastic leukemia	0	1 (3.7)
Unknown	20 (20.4)	10 (37.0)
Bone marrow aspirate prior to treatment initiation		
Performed, n (%)		
Yes	79 (80.6)	11 (40.7)
No	17 (17.3)	14 (51.9)
Unknown	2 (2)	2 (7.4)
Blast cell proportion		
n	76	11
Mean (SD)	44.2 (25.6)	35.5 (25.0)
Median (Q1-Q3)	39.5 (26-60)	33 (20-50)
Mono/poly-morphous, n (%)		
Monomorphous	5 (6.3)	1 (9.1)
Polymorphous	14 (17.7)	1 (9.1)
Unknown	60 (75.9)	9 (81.8)
Megakaryocytes, n (%)		
Present	31 (39.2)	7 (63.6)
Not identified	27 (34.2)	1 (9.1)
Unknown	21 (26.6)	3 (27.3)

py (9.21; 95% CI 4.7-11.8), followed by other medications (4.34; 95% CI 1.5-7.8), BSC treatment (1.38; 95% CI 0.9-5.3), and LDCA (1.33; 95% CI 0.3-9.1). Median PFS in months showed a similar trend, with patients treated with HMA having higher values (4.77; 95% CI 2.8-8.7) when compared with other medications (1.78; 95% CI 0.8-4.3), BSC only (1.25; 95% CI 0.6-2.6), and LDCA (1.33; 95% CI 0.2-9.1). Additionally, treatment failure was present for almost more than two-thirds of patients in both the LIC (n=76, 77.6%) and the BSC only (n=24, 88.9%) subgroups, with a median TTF in months that was higher for HMA-treated patients (3.81; 95% CI 2.1-5.4) followed by other medications (1.32; 95% CI 0.5-4.2), BSC only (0.99; 95% CI 0.8-2.5), and LDCA (0.23; 95% CI 0.1-0.3). When comparing Kaplan-Meier survival curves for OS, PFS, and TTF (**figure 1**), there were overall statistically significant differences among them (Log-rank test *p*-value <0.001).

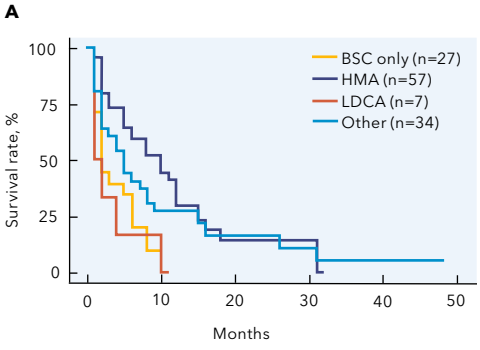
Tabla 3. Patient demographics and comorbidities for systemic therapy and best supportive care by country

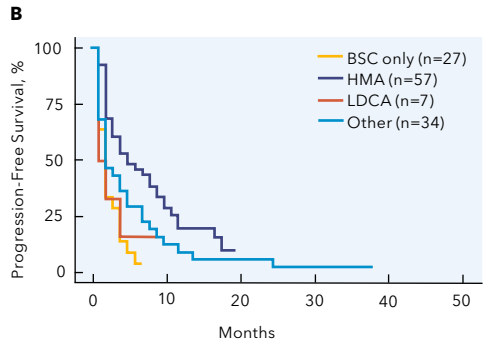
	Colombia (n=51)			Peru (n=59)		
	Total (n=51)	**LIC (n=41)**	**BSC only (n=10)**	**Total (n=59)**	**LIC (n=47)**	**BSC only (n=12)**
Demographics						
Sex (%)						
Male	28 (54.9)	23 (56.1)	5 (10.0)	33 (55.9)	26 (55.3)	7 (58.3)
Female	23 (45.1)	18 (43.9)	5 (10.0)	26 (44.1)	21 (44.7)	5 (41.7)
Age at diagnosis						
Mean (SD)	74.9 (8.39)	75.0 (8.64)	74.5 (7.68)	75.1 (7.9)	73.6 (7.68)	81.4 (5.50)
Median (Q1-Q3)	77 (70-81)	77 (71-81)	73.5 (68-81)	75 (68-83)	74 (68-80)	84 (72-88)
Comorbidities[a] (%)						
Myocardial infarction	3 (5.9)	2 (4.9)	1 (10.0)	-	-	-
Angina/coronary artery disease	6 (11.8)	3 (7.3)	3 (30.0)	1 (1.7)	1 (2.1)	0
Congestive heart failure	10 (19.6)	9 (22.0)	1 (10.0)	-	-	-
Arrhythmias	4 (7.8)	4 (9.8)	0	1 (1.7)	0	1 (8.3)
Restrictive lung disease or COPD	4 (7.8)	3 (7.3)	1 (10.0)	-	-	-
Renal failure or CKD stage 3, 4 or 5	1 (2.0)	1 (2.4)	0	-	-	-
Other	34 (66.7)	26 (63.4)	8 (80.0)	21 (35.6)	19 (40.4)	2 (16.7)
Unknown	5 (9.8)	5 (12.2)	0	16 (27.1)	7 (14.9)	9 (75.0)
None	8 (15.7)	7 (17.1)	1 (10.0)	19 (32.2)	19 (40.4)	0
Elevated transaminases (elevation not related to liver cirrhosis) or renal failure or CKD stage 3, 4	3 (5.9)	2 (4.9)	1 (10.0)	2 (3.4)	2 (4.3)	0

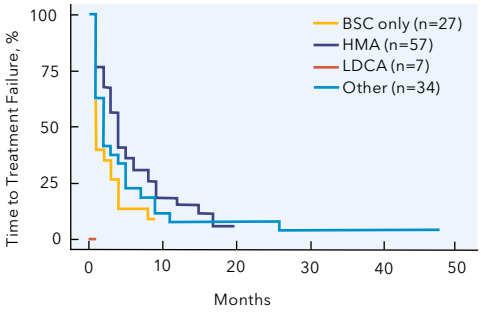
LIC: low-intensity chemotherapy; BSC: best supportive care; COPD: chronic obstructive pulmonary disese; CKD: chronic kidney disease.

[a] Percentages may sum up to more than 100% as multi-selection was allowed.

Regarding response rate per physician assessment, patients receiving LIC showed a mean time from the start of treatment to best response of 92.2 days (SD 93.3) defined as CR (n=11, 11.2%), CRi (n=1, 1%), PR (n=4, 4.1%), StD (n=17, 17.3%), or PD (n=29, 29.6%); however, there was no information for 36 patients (36.7%) due to loss of follow-up. For patients receiving BSC only, 9 (33.3%) showed PD, yet there was no information for the remaining 18 (66.7%) cases. Similarly, the mean time from the start of treatment to PD was 145 (SD 208.4) and 42.9 (SD 50.5) days for the LIC and the BSC-only subgroups, respectively. For LIC patients, the mean duration of CR/CRi/PR was 140.3 (SD 223.4) days.







D

Overall Survival	LDCA[a] (n=7)	HMA[a] (n=57)	Other[a] (n=34)	BSC only (n=27)
Censored[b], n (%)	1 (14.3)	22 (38.6)	8 (23.5)	5 (18.5)
Deaths, n (%)	6 (100)	35 (68.6)	26 (81.3)	22 (88.0)
Median survival in months (Q1-Q3)	1.33 (0.3-3.6)	9.21 (2.7-14.8)	4.34 (1.3-14.4)	1.38 (0.9-5.6)
Progression Free Survival				
Censored[b], n (%)	1 (14.3)	14 (31.6)	3 (8.8)	2 (14.8)
Deaths, n (%)	6 (100)	39 (73.6)	31 (93.9)	23 (92.0)
Median survival in months (Q1-Q3)	1.33 (0.3-3.6)	4.77 (1.4-11.8)	1.78 (0.8-4.3)	1.25 (0.3-3.5)
Time to Treatmente Failure				
Censored[b], n (%)	0	19 (33.3)	5 (14.7)	4 (14.8)
Deaths, n (%)	7 (100)	38 (79.2)	29 (90.6)	23 (95.8)
Median survival in months (Q1-Q3)	0.23 (0.2-0.3)	3.81 (1.1-8.6)	1.32 (0.5-4.9)	0.99 (0.3-3.9)

Figura 1. Kaplan-Meier survival curves. (A) Overall Survival (OS). (B) Progression Free Survival (PFS). (C) Time to Treatment Failure (TTF). (D) Corresponding risk tables.
[a] LDCA includes low-dose cytarabine; HMA includes 5-azacitidine (azacytidine) and decitabine; targeted therapies include FLT3 inhibitors, enasidenib, ivosidenib, and gemtuzumab ozogamicin; and other includes cytarabine, aclarubicin, G-CSF regimen (CA+G), enocitabine (BH-AC), combination of therapies, venetoclax, and other. Combination of therapies refers to therapies across different subgroups among LDCA, HMA, and targeted therapies.
[b] Patients who had not been reported as dead within the study observation period were censored on the study end date or the last contact date available in the dataset, whichever occurred first. BSC: best supportive care; CA+G: cytarabine, aclarubicin; G-CSF: granulocyte colony stimulating factor; HMA: hypomethylating agents; LDCA: low-dose cytarabine.

Treatment discontinuations were high in both LIC (n=89, 90.8%) and BSC only (n=25, 92.6%) subgroups; the mean duration of treatment until discontinuation was 102.1 (SD 129.1) days for the former and 66.1 (SD 83.7) days for the latter. The primary reason for treatment discontinuation was PD among LIC patients (n=33, 33.7%) and death among those on BSC only (n=20, 74.1%). Other relevant causes in the LIC subgroup included death (n=31, 31.6%), toxicity (n=9, 9.2%), a decline in performance status (n=18, 18.4%), insurance barriers (n=1, 1%), patient preference (n=10, 10.2%), completion of planned treatment (n=5, 5.1%), physician preference (n=2, 2%), other directly unre-

lated causes (n=4, 4.1%), and unknown cause (n=6, 6.2%). For the BSC-only subgroup, causes included PD (n=2, 7.4%), a decline in performance status (n=2, 7.4%), insurance barriers (n=1, 3.7%), patient preference (n=1, 3.7%), and completion of planned treatment (n=1, 3.7%). These values may sum up to more than the total of patients presented for each subgroup, as multi-selection was allowed.

Finally, for the 23 patients mentioned above who required a second line of treatment, among the LIC subgroup, there was a mean time from the start of treatment to the best response of 101.5 days (SD 28.6) being mainly StD (n=3, 27.3%) and PD (n=3, 27.3%) followed by PR (n=1, 9.1%); there was no information for four patients (36.4%) due to loss of follow-up. For the BSC-only subgroup, data was available for only one patient (8.3%) who showed PD. Treatment discontinuation was observed in 90.9% (n=10) of the LIC patients and 75% (n=9) of those in the BSC cohort. Reasons for discontinuation in the LIC subgroup included disease progression (n=4, 36.4%), death (n=3, 27.3%), toxicity (n=1, 9.1%), a decline in performance status (n=1, 9.1%), completed planned treatment (n=1, 9.1%), and of unknown cause (n=1, 9.1%); and in the latter, were death (n=7, 58.3%), disease progression (n=1, 8.3%), and unknown cause (n=1, 8.3%). Treatment failure was reported in 72.7% (n=8) and 66.7% (n=8) of LIC and BSC-only subgroups and showed a mean time to it of 79.4 (SD 61.5) and 36.9 days (SD 48.99), respectively.

Healthcare resource utilization

During the first line of treatment, 76 (77.6%) patients were hospitalized in the LIC subgroup and 17 (63%) in the BSC-only group, accounting for a total of 282 events (**table 4**). The median length of stay in days was longer for the LIC patients than for the BSC-only patients (10.5 [mean of 1.7 days in ICU] vs. 8 [mean of 2.7 in ICU]), and most were treatment administration- and infection-related for the former subgroup and infection- and transfusion-related for the latter (**table 4**).

As for the first hospitalization, the median length of stay in days was longer for the LIC patients 18 (mean of 34 ± 66.08 days and mean of 2.5 days in ICU) vs. 8 (mean of 14 ± 15.73 days and mean of 3.2 days in ICU) for the BSC-only patients, and the reasons included treatment administration (n=44, 57.9%), infection (n=35, 46.1%), relapse (n=29, 38.2%), transfusion support (n=20, 26.3%), and other AML-related or unrelated event (n=14, 18.4% and n=7, 9.2%). On the other hand, reasons for hospitalization among the BSC-only patients were relapse (n=7, 41.2%), infection (n=7, 41.2%), transfusion support (n=6, 35.3%), and other AML-related or unrelated event (n=4, 23.5% and n=2, 11.8%).

Regarding the second hospitalization, the median length of stay in days was equal for the LIC and the BSC-only patients 8; however, the mean length in days was higher for the former (29.4 ± 84.42 vs. 9.3 ±4.16). Only for LIC patients there was a third hospitalization reported (median length of stay of 12.5 and mean length of stay of 20.6 ± 22.29 days).

The percentage of patients requiring outpatient consultations and the mean number of visits were higher in the LIC subgroup than in the BSC-only subgroup (n=78, 79.6% vs. n=11, 40.7% and 11 [SD 13.5] vs. 7.9 [SD 7.4]). Transfusion support was given to 74.5% (n=73) and 81.5% (n=22) of LIC and BSC-only patients, respectively (**table 4**).

Tabla 4. Number and reasons for hospitalizations per type of first treatment

	LIC	BSC only
Number of hospitalizations per patient, n (%)	**n=76***	**n=17***
1	56 (73.7)	14 (82.4)
2	4 (5.3)	3 (17.6)
≥3	16 (21.1)	0
Reasons for all hospitalizations, n (%)	**n=148****	**n=20****
Progression/Relapse-related	41 (27.5)	7 (35)
Infection-related	65 (43.6)	8 (40)
Transfusion-related	37 (24.8)	8 (40)
Treatment administration-related	73 (49)	0
Other AML-related event	22 (14.8)	5 (25)
Other	13 (8.7)	3 (15)
Number of days hospitalized	**n=148****	**n=20****
Mean (SD)	25.5 (57.4)	13.3 (14.6)
Median (Q1–Q3)	10.5 (5.0-27.5)	8 (5.0-15.5)
Number of days in ICU	**n=145****	**n=20****
Mean (SD)	1.7 (6.04)	2.7 (6.40)
Median (Q1–Q3)	0 (0.0-0.0)	0 (0.0-2.5)
Outpatient consultations during the first line of treatment, n (%)		
Yes	78 (79.6)	11 (40.7)
No	18 (18.4)	15 (55.6)
If yes, number of visits	**n=77**	**n=11**
Mean (SD)	11.0 (13.47)	7.9 (7.38)
Median (Q1–Q3)	5 (3.0-14.0)	3 (2.0-16.0)
RBC/platelet transfusions, n (%)	65 (43.6)	8 (40)
Yes	73 (74.5)	22 (81.5)
No	22 (22.4)	5 (18.5)
Unknown	3 (3.1)	0
If yes, number of RBC transfusions	**n=65**	**n=21**
Mean (SD)	9.9 (9.98)	8.9 (8.43)
Median (Q1–Q3)	6 (3.0-14.0)	6 (3.0-12.0)
If yes, number of platelet transfusions	**n=62**	**n=20**
Mean (SD)	9.2 (16.58)	8.5 (11.00)
Median (Q1–Q3)	2 (0.0-8.0)	3.5 (0.5-13.5)

LIC: low-intensity chemotherapy; BSC: best supportive care; SD: standar deviation; RBC: red blood cells. * Patients, ** Hospitalizations.

Discussion

As mentioned in the introduction, the context of AML in Latin America is conditioned by factors inherent to the patient and their sociocultural context. This study set out with the aim of assessing, through real-world data, the need to shorten the knowledge gap concerning the current status and differences in the clinical course and therapy response of Latin American AML patients who are not eligible for intensive induction chemotherapy.

Whether a patient is or is not eligible for such intensive therapies is based on multiple factors, such as medical fitness, functionality, and comorbid illnesses, all of which are naturally associated with age. Prior studies have noted the importance of considering this group of patients with caution, not only because of their specific characteristics that may condition worse outcomes, but also because of the imminent aging processes among populations.

Consistent with the literature, this study found a mean age of 74.7 years, similar to the mean age (73.1 ±8 years) presented by Ma et al. on a real-world US-based survey for patients with AML [24]. Further, it is coherent with what was reported by Jaime-Perez et al. in 2022 [11] for a Mexican elderly AML population (median of 69 years); thus, being this publication one of the few focusing on elderly (most of them not eligible for intensive therapy) AML patients in our Latin American region. When comparing our results to other cohorts of Latin American AML patients without making the distinction of being not eligible for intensive induction chemotherapy, there are a few differences: e.g., for 2021 and 2022, Silveira et al. and Rodrigues et al. in Brazil report younger median ages in ranges of 45 to 54 years [25,26].

Interestingly, other publications on Latin American patients (Mexico), such as Jaime-Pérez et al. in 2014 found the median age at diagnosis of AML to be 32 years [17], supporting the fact that AML patients tend to be younger in this region. There is also a study reporting results on AML adult Colombian patients and one on AML adult Peruvian patients; however, there was use of intensive induction chemotherapy in 96.2% and 100% of cases, respectively, thus, not being comparable to our study's context [27,28]. Another publication on Peruvian AML patients, showed a median age at diagnosis of 44, but it did not have any information regarding treatment approaches [29].

Among patients on LIC, cardiovascular and lung diseases were less common (18.4% vs. 33.3% and 3.1% vs. 7.4%); however, patients suffering from elevated transaminases (not related to liver cirrhosis) or renal failure/CKD 3 or 4 were more frequent (8.2% vs. 3.7%). Even though mean ages were similar (74.4 vs. 76), the minimum age for patients on BSC-only therapy was higher (62 vs. 41). ECOG 0-1 status was more frequent in LIC patients (36.7% vs. 22.2%); yet, a status of 2 and 3 were remarkably frequent in the LIC and BSC-only subgroup, respectively (29.6% and 25.9%). These results may help us to indirectly understand the reasons behind the physicians therapeutical decision-making process and to raise awareness on the ineligibility criteria for intensive induction chemotherapy.

The overall hospitalization rate was slightly higher in our population compared with that reported in a US claim-based analysis of AML patients treated with 5-azacitidine (74.4% vs. 61.5%);

nevertheless, the reason for hospitalizations was similar when considering infection-related causes (43.6% vs. 46.6-47.1%) [30]. The study by Jaime-Perez et al. of elder Mexican AML patients reported a median length of stay for patients receiving LDCA of 5 days (Min-Max 4-10) [11]; another study in US hospitals reported a median length of stay of 5.8 days, being longer in patients younger than 60 years (6.8 vs. 5.4 days) [31]. Both studies report relatively lower length of stays than what we obtained (10.5 days); however, a possible explanation for these results may be the differences not only in the sociocultural context of the participating sites, but also in our aforementioned inclusion criteria.

For the BSC-only subgroup no patients reported ≥ 3 hospitalizations. The mean length of inpatient stay was higher for the LIC subgroup (25.5 vs. 13.3 days) as well as the mean number of outpatient visits during the first line of treatment (11 vs. 7.9). On the other hand, there was a trend towards a lower relative number of patients requiring transfusions during the first line of treatment for the LIC patients (74.5% vs. 81.5%). These findings are related to an inherent difference between the intention of both treatments and might indicate a restrictive or limited effort approach for the BSC-only patients. An implication for further research is the potential impact in the resource's utilization and economic burden differences between LIC and BSC-only.

Turning now to our study's outcomes, the median OS was the longest among patients receiving HMA (9.2 months, Min-Max 0.62-30.51), which is in line not only with data reported by previous studies [32,33] but also with the current general recommendations of treatment for older adults with AML [10]. The median OS in our BSC-only subgroup was 1.4 months (Min-Max 0.07-8.47), consistent with the study conducted by Heiblig et al. (median OS 2.6 months) [34]. Also, the median PFS and TTF were approximately four times longer in the patients receiving HMA compared with other treatments (LDCA and BSC-only), supporting previous research into this area not only in Latin America but also in other populations [32,35,36].

Our results also indicate that the LIC was the preferred choice over BSC-only in patients who were not eligible for intensive induction chemotherapy (78.4% versus 21.6%). In the US community oncology practices in elderly patients with AML, 57% of patients received systemic therapy, while 43% received BSC [24], just as in our study BSC only was not the preferred choice. In another real-world study from India, 23% of elderly AML patients were on BSC [33], similar to the observations in our study. In contrast, LIC was the choice of treatment only in 33.1% of elderly AML patients (aged ≥70 years) in a French real-world study [34]. HMA (5-azacitidine) was the most common first-line treatment in our study (55.1% patients), congruent with the large data analysis published by Medeiros et al. among elderly patients with AML in the US, wherein 73.6% of patients received HMA-based treatment [21].

A possible explanation for this might be that the decision-making process for AML patients who are not eligible for intensive induction chemotherapy in the participating sites, Colombia, Peru, and Panama, is guided by both the National Comprehensive Cancer Network recommendations [9] and Colombian and Peruvian local treatment guidelines (applicable at the time that the study was conducted). This guidelines recommended considering treatment either with LDCA, 5-azacitidine, or BSC under

this scenario [37,38]. Nevertheless, it is important to bear in mind the possible bias in these comparisons. First, due to the lack of standardized terminology to name patients not eligible for intensive induction chemotherapy, finding terms such as: "unfit", "medically unfit", "frail", "ineligible", or even, in some cases, "elderly" (considering that age solely is not a cause of ineligibility). And second, due to the need for explicit criteria to define a patient as not eligible, with some authors/clinical trials recently proposing their own objective standards for such designation, in contrast to the premise of the physician's subjective appraisal of certain variables as a decision-making tool [14,39].

The generalizability of these results is subject to certain limitations. For instance, the small sample size, which may be explained by the low incidence of the disease, and the unavoidable loss of follow-up, loss of insurance coverage, health system fragmentation, and incomplete information (inherent to real-world studies) affects the needed statistical power to guarantee the assessment of potential hypothesis and more complex inferential analysis (i.e., the causal effect of interventions when controlling for certain confounders). Additionally, the lack of studies reporting on this specific subgroup of patients in Colombia, Peru, or Panama difficult the potential for comparisons; regardless, it highlights the novelty of our research. Finally, a note of caution is due when comparing our findings considering our inclusion criteria, thus, encouraging the understanding of this not eligible for intensive therapy subpopulation for future real-world-based research in Latin America.

Notwithstanding these limitations, this study offers a real-world-based insight into the treatment patterns and clinical outcomes in Latin American AML patients who are not eligible for intensive induction chemotherapy. We found that generally, there is a preference for LIC as first-line treatment, being HMA/azacytidine the most common choice and the one with better results in terms of having a higher median OS, PFS, and TTF than those receiving BSC alone, LDCA, or another single/combination treatment. Our findings make several contributions to the current local literature to pave the first steps on the way to describe, understand, and support treatment recommendations, encouraging informed clinical decision-making processes. Further work needs to be done to validate our findings and to help us establish a greater degree of accuracy on this matter to paint a comprehensive picture of the disease and this subgroup of patients in Latin America.

Acknowledgments: The authors wish to thank IMAT Oncomédica's Patients. Andrés Borda, M.D., Myriam Lucía Rodríguez, MD., Lina María Abenoza, MD., Daniela Rodríguez, MD. and Laura Mendoza, MD. of the Fundación Santa Fe de Bogotá. All collaborators from Centro Hemato-Oncológico Panamá. The authors would like to thank Vibha Dhamija and Ananya Chikramane from IQVIA for their writing and editing support.

Ethical considerations: The study was conducted in compliance with the local regulations and was approved by the local institutional ethics committee in each country.

Funding: This work was supported by AbbVie Pharmaceuticals.

Data availability statement: All data generated or analyzed during this study are included in this published article (and its supplementary information files).

References

1. **Döhner H, Weisdorf DJ, Bloomfield CD.** Acute myeloid leukemia. N Engl J Med 2015;373:1136-1152. https://doi.org/10.1056/NEJMra1406184.
2. **American Cancer Society.** Key statistics for acute myeloid leukemia (AML). Georgia, Estados Unidos: American Cancer Society; 2021. Available from https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html.
3. **Dong Y, Shi O, Zeng Q, Lu X, Wang W, Li Y, et al.** Leukemia incidence trends at the global, regional, and national level between 1990 and 2017. Exp Hematol Oncol 2020;9:14. https://doi.org/10.1186/s40164-020-00170-6.
4. **Yi M, Li A, Zhou L, Chu Q, Song Y, Wu K.** The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: estimates based on the global burden of disease study 2017. J Hematol Oncol 2020;13:72. https://doi.org/10.1186/s13045-020-00908-z.
5. **United Nations (UN).** World population ageing. New York, USA: United Nations, Department of Economic and Social Affairs; 2019. Available from https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Report.pdf.
6. **Ou Z, Yu D, Liang Y, He W, Li Y, Zhang M, et al.** Analysis of the Global Burden of Disease study highlights the trends in death and disability-adjusted life years of leukemia from 1990 to 2017. Cancer Commun (Lond) 2020;40:598-610. https://doi.org/10.1002/cac2.12094.
7. **Bewersdorf JP, Shallis RM, Wang R, Huntington SF, Perreault S, Ma X, et al.** Healthcare expenses for treatment of acute myeloid leukemia. Expert Rev Hematol 2019;12:641-650. https://doi.org/10.1080/17474086.2019.1627869.
8. **Gao L, Nguyen D, Lee P.** A systematic review of economic evaluations for the pharmaceutical treatment of chronic lymphocytic leukemia and acute myeloid leukemia. Expert Rev Hematol 2022;15:833-847. https://doi.org/10.1080/17474086.2022.2125376.
9. **Tallman MS, Wang ES, Altman JK, Appelbaum FR, Bhatt VR, Bixby D, et al.** Acute myeloid leukemia, version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:721-749. https://doi.org/10.6004/jnccn.2019.0028.
10. **Sekeres MA, Guyatt G, Abel G, Alibhai S, Altman JK, Buckstein R, et al.** American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv 2020;4:3528-3549. https://doi.org/10.1182/bloodadvances.2020001920.
11. **Jaime-Pérez JC, Ramos-Dávila EM, Picón-Galindo E, Jiménez-Castillo RA, León AG, Gómez-Almaguer D.** Outcomes and survival predictors of Latin American older adults with acute myeloid leukemia: Data from a single center. Hematol Transfus Cell Ther 2022;25:S2531-1379(2522)00010-00014. https://doi.org/10.1016/j.htct.2022.01.003.
12. **Griffiths EA, Carraway HE, Chandhok NS, Prebet T.** Advances in non-intensive chemotherapy treatment options for adults diagnosed with acute myeloid leukemia. Leuk Res 2020;91:106339. https://doi.org/10.1016/j.leukres.2020.106339.
13. **Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al.** Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-447. https://doi.org/10.1182/blood-2016-08-733196.
14. **Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, et al.** Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood 2020;135:2137-2145. https://doi.org/10.1182/blood.2020004856.
15. **Wei AH, Strickland SA, Hou JZ, Fiedler W, Lin TL, Walter RB, et al.** Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: Results from a phase Ib/II study. J Clin Oncol 2019;37:1277-1284. https://doi.org/10.1200/jco.18.01600.
16. **Abbvie Inc.** Prescribing Information, VENCLEXTA® (venetoclax tablets) Approved by U.S. Food and Drug Administration. Illinois,

USA: Abbvie Inc.; 2019. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208573s013lbl.pdf

17. **Jaime-Pérez JC, Brito-Ramirez AS, Pinzon-Uresti MA, Gutiérrez-Aguirre H, Cantú-Rodríguez OG, Herrera-Garza JL, et al.** Characteristics and clinical evolution of patients with acute myeloblastic leukemia in northeast Mexico: an eight-year experience at a university hospital. Acta Haematol 2014;132:144-151. https://doi.org/10.1159/000356794.
18. **Padilha SL, Souza EJ, Matos MC, Domino NR.** Acute myeloid leukemia: survival analysis of patients at a university hospital of Paraná. Rev Bras Hematol Hemoter 2015;37:21-27. https://doi.org/10.1016/j.bjhh.2014.11.008.
19. **Meillon-Garcia LA, Demichelis-Gómez R.** Access to therapy for acute myeloid leukemia in the developing world: Barriers and solutions. Curr Oncol Rep 2020;22:125. https://doi.org/10.1007/s11912-020-00987-8.
20. **Vaughn JE, Shankaran V, Walter RB.** Trends in clinical benefits and costs of novel therapeutics in aml: At what price does progress come? Curr Hematol Malig Rep 2019;14:171-178. https://doi.org/10.1007/s11899-019-00510-2.
21. **Medeiros BC, Pandya BJ, Hadfield A, Pike J, Wilson S, Mueller C, et al.** Treatment patterns in patients with acute myeloid leukemia in the United States: a cross-sectional, real-world survey. Curr Med Res Opin 2019;35:927-935. https://doi.org/10.1080/03007995.2019.1578152.
22. **Zeidan AM, Wang R, Wang X, Shallis RM, Podoltsev NA, Bewersdorf JP, et al.** Clinical outcomes of older patients with AML receiving hypomethylating agents: a large population-based study in the United States. Blood Advances 2020;4:2192-2201. https://doi.org/10.1182/bloodadvances.2020001779.
23. **DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, et al.** Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. The Lancet Oncology 2018;19:216-228. https://doi.org/10.1016/S1470-2045(18)30010-X.
24. **Ma E, Bonthapally V, Chawla A, Lefebvre P, Swords R, Lafeuille MH, et al.** An evaluation of treatment patterns and outcomes in elderly patients newly diagnosed with acute myeloid leukemia: A retrospective analysis of electronic medical records from US community oncology practices. Clin Lymphoma Myeloma Leuk 2016;16:625-636.e623. https://doi.org/10.1016/j.clml.2016.08.006.
25. **Rodrigues AL, do Nascimento DM, de Lima JM, Reis ML, Leão LB, Azevedo MC, et al.** Safety and feasibility of outpatient high dose cytarabine for acute myeloid leukemia in the Brazilian Amazon. Int J Hematol Oncol Stem Cell Res 2020;14:151-156. https://doi.org/10.18502/ijhoscr.v14i3.3722.
26. **Silveira DR, Coelho-Silva JL, Silva WF, Vallance G, Pereira-Martins DA, Madeira MI, et al.** A multicenter comparative acute myeloid leukemia study: can we explain the differences in the outcomes in resource-constrained settings? Leuk Lymphoma 2021;62:147-157. https://doi.org/10.1080/10428194.2020.1827252.
27. **Díaz-Correa LM, Madrid-Muñoz CA, Combariza-Vallejo JF, Gálvez-Cárdenas KM, Olaya-Colorado V, Donado-Gómez JH.** Supervivencia de los pacientes adultos con leucemia mieloide aguda en el departamento de hematología del Hospital Pablo Tobón Uribe entre los años 2004 y 2010. Rev Col Hematol Oncol 2017;4:40. https://doi.org/10.51643/22562915.236.
28. **Lovato PE.** Leucemia mieloide aguda en adultos: Estudio comparativo sobre tratamiento y pronóstico por grupos etarios. Rev Med Hered 2015;26:160-166.
29. **Al-kassab-Córdova A, Lachira-Yparraguirre L, Sandival-Ampuero G, Roque K, Ortega E, Lozano-Ballena S, et al.** Incidence and outcome of acute myeloid leukemia in Peru: An 11-year single center experience. Blood 2020;136:28-29. https://doi.org/10.1182/blood-2020-143373.
30. **Smith BD, Beach CL, Mahmoud D, Weber L, Henk HJ.** Survival and hospitalization among patients with acute myeloid leukemia treated with azacitidine or decitabine in a large managed care population: a real-world, retrospective, claims-based, comparative analysis. Exp Hematol Oncol 2014;3:10. https://doi.org/10.1186/2162-3619-3-10.

31. **Kumar AJ, Henzer T, Rodday AM, Parsons SK.** Risk factors for length of stay and charge per day differ between older and younger hospitalized patients with AML. Cancer Med 2018;7:2744-2752. https://doi.org/10.1002/cam4.1492.
32. **Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al.** International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015;126:291-299. https://doi.org/10.1182/blood-2015-01-621664.
33. **Kanakasetty GB, Lakshmaiah KC, Dasappa L, Jacob LA, Suresh-Babu MC, Lokesh KN, et al.** Treatment patterns and comparative analysis of non-intensive regimens in elderly acute myeloid leukemia patients-a real-world experience from India. Ann Hematol 2019;98:881-888. https://doi.org/10.1007/s00277-019-03600-6.
34. **Heiblig M, Le Jeune C, Elhamri M, Balsat M, Tigaud I, Plesa A, et al.** Treatment patterns and comparative effectiveness in elderly acute myeloid leukemia patients (age 70 years or older): the Lyon-university hospital experience. Leuk Lymphoma 2017;58:110-117. https://doi.org/10.1080/10428194.2016.1180688.
35. **Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al.** Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223-232. https://doi.org/10.1016/s1470-2045(09)70003-8.
36. **Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al.** Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012;30:2670-2677. https://doi.org/10.1200/jco.2011.38.9429.
37. **Ministerio de Salud.** Guía de Práctica Clínica. Leucemia mieloide aguda. Lima, Perú: Instituto Nacional de Enfermedades Neoplásicas; 2011. Available from https://www.inen.sld.pe/portal/documentos/pdf/normas_tecnicas/2011/20102011_LEUCEMIA_MIELOIDE_AGUDA.pdf.
38. **Ministerio de Salud y Protección Social.** Guía de práctica clínica (GPC) para la detección, tratamiento y seguimiento de leucemias linfoblástica y mieloide en población mayor de 18 años. Guía No. GPC 2017-34. Bogotá D.C., Colombia: Ministerio de Salud y Protección Social; 2017. Available from http://gpc.minsalud.gov.co/gpc_sites/Repositorio/Conv_563/GPC_Leucemia_Mayores_18a%C3%B1os/GPC_Leucemias.pdf.
39. **Qin Y, Kuang P, Liu T.** Venetoclax combined with hypomethylating agents or low-dose cytarabine as induction chemotherapy for patients with untreated acute myeloid leukemia ineligible for intensive chemotherapy: a systematic review and meta-analysis. Clin Exp Med 2022;23:219-222. https://doi.org/10.1007/s10238-021-00784-y.