CAMbios. 2024, v.23 (2): e910

[1]Andrés Orquera Carranco, Hospital de Especialidades Carlos Andrade Marín, Unidad Técnica de Hematología. Quito-Ecuador. E mail: andreshemato2015@gmail.com. ORCID ID: https://orcid.org/0000-0003-0143-2967.
[2]Siboney Loayza Salazar, Hospital de Especialidades Carlos Andrade Marín, Unidad Técnica de Hematología. Quito-Ecuador. E mail: zoila.loayza@iess.gob.ec. ORCID ID: https://orcid.org/0000-0001-9658-5004.
[3] Leonardo Mendieta Carrión, Universidad Central del Ecuador, Quito-Ecuador. E mail: leofmc95@hotmail.com. ORCID ID: https://orcid.org/0000-0002-0883-3811
[4]David Garrido Salazar, Hospital de Clínicas "Dr. Manuel Quintela", Unidad de Hematología. Montevideo-Uruguay. E mail: david0labinmuno@gmail.com. ORCID ID: https://orcid.org/0000-0002-7384-1236
[5]Jhony Carranza Jara, Hospital Provincial Pablo Arturo Suarez, Unidad de Hematología. Quito-Ecuador. E mail: carranzajhonny@hotmail.com. ORCID ID: https://orcid.org/0000-0002-9893-0681
[6] Paola Velasco Maldonado, Hospital de Especialidades Carlos Andrade Marín, Unidad Técnica de Hematología. Quito-Ecuador. E mail: paola.velasco@iess.gob.ec. ORCID ID: https://orcid.org/0000-0002-5915-9177
[7] Alejandra Ramírez Lozada, Universidad Central del Ecuador, Quito-Ecuador. E mail: Ale_ramirez.l@hotmail.com. ORCID ID: https://orcid.org/0000-0002-0883-3811

Correspondencia autor:

Dr. Andrés Orquera Carranco
Eustorgio Salgado.
E mail: andreshemato2015@gmail.com
Quito-Ecuador
Postal Code: 17521
Phone: (593) 999047462

CAMbios
https://revistahcam.iess.gob.ec/index.php/cambios/issue/archive
e-ISSN: 2661-6947
Periodicidad semestral: flujo continuo
Vol. 23 (2) Jul-Dic 2024
revista.hcam@iess.gob.ec
DOI: https://doi.org/10.36015/cambios.v23.n2.2024.910

ORIGINAL STUDY: OBSERVATIONAL STUDY

Survival analysis of acute promyelocytic leukemia in a third-level hospital in Ecuador.

Análisis de supervivencia de leucemia promielocítica aguda en un hospital de tercer nivel en el Ecuador

Andrés Orquera Carranco[1], Siboney Loayza Salazar[2], Leonardo Mendieta Carrión[3], David Garrido Salazar[4], Jhony Carranza Jara[5], Paola Velasco Maldonado[6], Alejandra Ramírez Lozada[7].

Recibido: 21-05-2023 Aprobado: 07-04-2023 Publicado: 25-11-2024

ABSTRACT

INTRODUCTION. There is an important number of reports in Latin America, but there is a lack of data on acute promyelocytic leukemia (APL) in Ecuador., this is the main reason to carry out this study in the country, a disease that in recent decades has shown a significant improvement in survival. OBJECTIVES. To evaluate the overall survival (OS) and event-free survival (EFS), and also the demography, and the most relevant clinical and laboratorial findings. METHODS. We retrospectively reviewed the medical records of 48 patients with APL, diagnosed between January 2012 and December 2019. We collected the most relevant demographic, clinical and laboratorial characteristics, as well as data related to 30-day mortality, and 5 year–OS (overall survival) and EFS (event-free survival). RESULTS. Among the forty-eight (48) patients with acute promyelocytic leukemia, 44 patients received treatment, the mean number of days for the start of all trans retinoic acid (ATRA) and/or arsenic trioxide (ATO) was of 2.5 days from the moment of the diagnosis. 60.4% of patients were classified as low risk and 39.5% as high risk, according to the national comprehensive cancer network (NCCN). The early death rate was 31.2%, the main cause of which was sepsis, multidrug resistant (MDR) bacterias were isolated in 83% of the patients who took blood cultures and died of early sepsis. after a median follow-up of 35 months only one patient relapsed. the five-year OS and EFS was 51.2%; In the multivariate analysis, only age was identified as an adverse prognostic factor. DISCUSSION. Compared to prospective trials with ATRA-based regimens, we found an inferior OS, mainly because of a high-rate early death. if we compare our findings with other real-world reports, we will also show inferior results probably explained by the high rate of early death due to infection by MDR batteries, in addition to the early deaths caused by hemorrhages. CONCLUSION. The low rate of OS shown in this study, could be improved based on changes to optimize the access of the patients to an early diagnosis and treatment and the reduction of the unacceptably high rates of multidrug resistance bacterial infections in our setting.

Keywords: Leukemia, Promyelocytic, Acute; Survival; Sepsis; Drug Resistance, Multiple, Bacterial; Bacterial Infections; Carbapenem-Resistant Enterobacteriaceae.

RESUMEN

INTRODUCCION. Existe un número importante de reportes en Latinoamérica, pero se carece de datos sobre la leucemia promielocítica aguda (LPA) en Ecuador, ésta es la principal razón para realizar este estudio en el país, enfermedad que en las últimas décadas ha mostrado una importante mejoría en la sobrevida. OBJETIVOS. Evaluar la sobrevida global (SG) y la sobrevida libre de eventos (SLE), así como la demografía y los hallazgos clínicos y laboratoriales más relevantes. MÉTODOS. Se revisaron retrospectivamente las historias clínicas de 48 pacientes con LPA, diagnosticados entre enero de 2012 y diciembre de 2019. Se recogieron las características demográficas, clínicas y datos de laboratorio más relevantes, así como datos relacionados con la mortalidad a 30 días, y a 5 años-OS (supervivencia global) y EFS (supervivencia libre de eventos). RESULTADOS. De los cuarenta y ocho (48) pacientes con leucemia promielocítica aguda, 44 pacientes recibieron tratamiento, la media de días para el inicio de ácido transretinoico total (ATRA) y/o trióxido de arsénico (ATO) fue de 2,5 días desde el momento del diagnóstico. El 60,4% de los pacientes fueron clasificados como de bajo riesgo y el 39,5% de alto riesgo, según la red nacional integral del cáncer (NCCN). La tasa de mortalidad precoz fue del 31,2%, cuya causa principal fue la sepsis, aislándose bacterias multirresistentes (MDR) en el 83% de los pacientes que se sometieron a hemocultivos y fallecieron por sepsis precoz. Tras una mediana de seguimiento de 35 meses, sólo un paciente sufrió una recaída, la SG y la SSC a cinco años fue del 51,2%; en el análisis multivariante, sólo la edad se identificó como factor pronóstico adverso. DISCUSIÓN. En comparación con los ensayos prospectivos con regímenes basados en ATRA, encontramos una SG inferior, principalmente debido a una alta tasa de muerte temprana. Si comparamos nuestros hallazgos con otros informes del mundo real, también mostraremos resultados inferiores probablemente explicados por la alta tasa de muerte temprana debida a infección por baterías MDR, además de las muertes tempranas causadas por hemorragias. CONCLUSIONES. La baja tasa de SG mostrada en este estudio, podría mejorarse en base a cambios para optimizar el acceso de los pacientes a un diagnóstico y tratamiento precoz y la reducción de las inaceptablemente altas tasas de infecciones bacterianas multirresistentes en nuestro medio.

Palabras clave: Leucemia Promielocítica Aguda; Sobrevida; Sepsis; Farmacorresistencia Bacteriana Múltiple; Infecciones Bacterias; Enterobacteriaceae Resistentes a los Carbapenémicos

INTRODUCTION

Acute promyelocytic leukemia (APL) also known in the French-American-British (FAB) classification as M3 acute myeloid leukemia (AML), and as AML with recurrent genetic alteration PML::RARA in the 2022 WHO update, is characterized by a severe hemorrhagic phenotype which carries a high risk of early death (ED), making it a hematological emergency[1,2]. However, the survival of APL patients has improved enormously since the introduction of drugs such as all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO), both used in combination as a chemo-free regimen or in association with conventional chemotherapy, allowing the differentiation promyelocytes, reaching a complete remission of the disease, and reverting the coagulopathy in a more effective way than never before. These achievements are considered milestones of hematology as reduced the early-mortality rates and improved overall survival (OS) and event-free survival (EFS) of the affected patients in the last decades[3,4].

Undoubtedly the therapy based on ATRA and ATO allows the avoidance of anthracycline-related toxicity. Particularly in Ecuador, based on the availability of the drugs, the most common induction therapy used is based on the combination of ATRA and chemotherapy. However, there is no permanent availability of these drugs in reference centers, provoking frequent delays in the start of treatment. Also, it is important to highlight the reduced availability of specialized centers in the country which causes a prolonged time between the disease debut and the specialized consultation[5].

To this context must be added the high rate of multidrug-resistant (MDR) bacterial infection, which presumably increases the treatment-related mortality observed in the induction phase of AML, a phenomenon that could particularly affect the survival rate of these type of cancer in our local setting.

Clinical trials conducted by diverse groups including the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and the Programa Español de Tratamientos en Hematología (PETHEMA)[6,7], reported rates of ED between 2.8-6.8%, These rates are hardly observed in studies based in the elderly population or in patients with comorbidities by the time of diagnosis, and even less in countries with less evolved health systems who have accessibility issues in the attention and management of APL (acute promyelocytic leukemia), as is mentioned by the International Consortium on Acute Promyelocytic Leukemia (IC-APL)[8].

In this context, there is an important number of reports in Latin America, but there is a lack of studies in Ecuador, this is the main reason to carry out this retrospective study in patients with acute promyelocytic leukemia treated in a third-level hospital, with the objectives of evaluating the 5-year OS and EFS rate, as well as, describe the demographic and the most relevant clinical and laboratory findings in patients with acute promyelocytic leukemia.

METHODS

Study design and Patients

We performed an observational, analytical, longitudinal, and retrospective study conducted at the Carlos Andrade Marín Hospital, Quito-Ecuador, included all patients with a diagnosis of APL confirmed by the presence of the chromosomal translocation t(15;17)(q22;q12);(PML::RARA), either by identification of the PML::RARA transcript by reverse transcriptase polymerase chain reaction (RT-PCR) or by fluorescence in situ hybridization (FISH). For those in whom translocation detection could not be performed (due to the momentary unavailability of RT-PCR or FISH), the diagnosis was based on the clinical and laboratory characteristic along with cytomorphological evaluation and immunophenotyping by flow cytometry.

Patients with >20% of missing data in the medical records, without evidence of t(15;17) (q22;q12);(PML::RARA) by RT-PCR or FISH, and patients unwilling to receive treatment were excluded.

The information corresponding to the patients included was collected by reviewing the electronic medical records.

The variables obtained included: age, sex, region of origin, and laboratory values at diagnosis such as blood biometry, fibrinogen, and coagulation profile to define the risk of disseminated intravascular coagulation (DIC). Additionally, we included the occurrence of adverse events or complications. Patients from the years 2020 and 2021, years of the SARS-CoV2 pandemic, were not included.

Treatment

In accordance with the standard practice of the Hematology Unit and the guidelines of the National Comprehensive Cancer Network (NCCN)[9], patients received an induction cycle based on the use of idarubicin 12 mg/m^2 or daunorubicin 60 mg/m^2 every other day for 4 doses, together with ATRA 45 mg/m^2 daily in divided doses and doses of 25 mg/m^2 if they were adolescent patients or children. Subsequently, three monthly cycles of consolidation with ATRA, anthracyclines, and Ara-C were continued according to the patient's risk and age.

All patients regardless of risk group after the consolidation phase received methotrexate, 6-mercaptopurine and ATRA as maintenance agents for 2 years.

Patients who could not be treated with ATRA due to lack of availability at our center at the time of diagnosis were started on anthracyclines as induction chemotherapy until it became available.

Usually, patients in the high-risk group did not receive intrathecal chemotherapy as central nervous system (CNS) prophylaxis. Additionally, transfusion support was given to all patients to maintain platelet levels >50,000/mm3 and cryoprecipitate was used to maintain fibrinogen at >150 mg/dl. Antibiotic and antifungal prophylaxis for neutropenia was administered with amoxicillin/clavulanic acid and fluconazole.

Study assessments and definitions

OS was calculated from the date of diagnosis to the date of death from any cause or date of last control and SLE was defined as the time from diagnosis of APL to the first occurrence of an event (failure to achieve complete response [CR], as would be demons

trated by detection of the PML::RARA fusion gene in RT-PCR analysis, relapse of disease after achieving CR or death from any cause). In the maintenance phase, response to treatment was evaluated every 3 months by complete blood count, and RT-PCR follow-up was generally not performed.

CR was defined as reaching a normalized PML-PML::RARA transcript level below the RT-PCR detection limit at the end of the consolidation phase. Disease relapse was defined as evidence of hematologic alterations plus PCR detection of the PML::RARA fusion gene in a patient with previously confirmed CR. Disease risk assessment was based on that recommended by the NCCN9, defining high risk as patients with ≥10,000/mm3 leukocytes and low risk as those with at diagnosis <10,000/mm3 leukocytes. Early death (ED) was defined as death within 30 days of APL diagnosis. Time-to-diagnosis (TTD) was defined as the time elapsed in days from symptom onset to diagnosis.

Statistical Analysis

Absolute and relative frequencies of the clinical-demographic data were described. Pearson's chi-square or Fisher's exact test was used for categorical variables. OS and EFS were evaluated at 5 years, using the Kaplan-Meier method, and for comparison between groups by Long Rank test; multivariate evaluation of factors associated with OS was conducted using the Cox proportional hazard regression model, the effect size on outcome was presented as Hazar Ratio (HR). All analyses were conducted using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

RESULTS

During the period of this study, 310 patients were diagnosed with AML, of these, 51 (16.4%) patients had a diagnosis of APL. Of the 51 patients with APL, one patient who was negative for detection of t (15;17) (q22;q12);(PML::RARA) and two patients who did not want treatment were excluded from the analysis.

Forty-eight patients were included in the analysis (including 2 pediatric patients), having a mean age 39.9 years (± 17.3 SD). Excluding the two pediatric patients (2 and 12 years), the mean age was 41.3 years (± 17.3 SD). Seventeen (35.4%) patients were females and 31 (64.5%) males; only one patient was categorized as secondary APL (the patient had received chemotherapy for breast cancer previously). Six patients did not undergo t (15;17) (q22;-q12);(PML::RARA) at debut, 3 patients due to lack of availability of RT-PCR/FISH in our center and 3 patients because they died before the sample could be sent to confirm the diagnosis, the diagnosis in these patients was made based on cytomorphology, immunophenotype by flow cytometry and fibrinogen level (all 6 patients had fibrinogen levels less than 150mg/dl; 5 patients died early. 1 died of infection and 4 died of central nervous system hemorrhage). The mean fibrinogen level in the whole group was 140,8 mg/dl (19-481). No patient debuted with extramedullary infiltration and the mean TTD was 14 days. Only one patient with APL had Afroecuadorian ethnicity, and the rest of the patients belonged to the mestizo ethnic group. The clinical demographic data are summarized in Table 1.

Table 1. General characteristics of patients

Variable	n	(%)
APL	48	(100)
Age group		
>15 years	46	(95,8)
>60 years	8	(16,6)
Gender		
Female	17	(35,4)
Male	31	(64,6)
APL de Novo	47	(97,9)
APL Secondary to chemotherapy*	1	(2,1)
Risk group **		
Low	29	(60,4)
High	19	(39,5)
DIC	15	(31,9)
DIC and low risk	9	
DIC and high risk	6	

***Patient with breast cancer treated with chemotherapy. **Risk assessment according to the National Comprehensive Cancer Network Guidelines. APL Acute Promyelocytic Leukemia, DIC Disseminated Intravascular Coagulation**.

Regarding treatment distribution, 44 (91.6%) patients received treatment and 4 (8.3%) of them died before starting onco-specific treatment (3/4 patients were high risk), 22 (45.8%) patients started ATRA and/or ATO on the day of cytomorphologic diagnosis, with an average number of days to start treatment of 2.5 days. 35 (75.9%) patients received chemotherapy together with ATRA and/or ATO. Table 2 specifies the type of treatment received. All patients who completed the consolidation phase continued with the maintenance phase for 2 years with ATRA, 6-mercaptopurine, and methotrexate, regardless of risk group. Table 2.

Adverse events

From the total of patients in our study, 15 (31.2%) patients died early, this subgroup of patients had a mean age of 52.3 years (± 17.3 SD). Eight (16.6%) died from infections (blood cultures were taken in 6/8 patients, and carbapenemase-producing Klebsiella were isolated in 5 patients [83.%]), 5 died from CNS hemorrhage; 1 died due to interalveolar hemorrhage and in 1 patient the cause was not determined; from the 6 (12.5%) patients who died from bleeding, 1 died on the same day of diagnosis, 4 patients died between the sixth and eighth day after diagnosis, and 1 patient died 21 days after diagnosis, the average number of days of diagnostic opportunity in this subgroup was 14 days. All patients who died from infections died after day 14 of diagnosis and the average number of days of diagnostic opportunity in patients who died from infections was 16 days. 4 patients did not receive treatment due to the lack of availability of ATRA in the institution, this subgroup of patients died on days 1,7,8, and 33 since diagnosis, and had a diagnostic opportunity of 15,10,11, and 29 days respectively. Also, 22 (45.8%) patients required intensive care unit (ICU) within the first 30 days of diagnosis (15/22 [68.1%] of them died in ICU). No difference was found when comparing the 30-day mortality rates from diagnosis in

Table 2. Types of induction treatment received by patients with acute promyelocytic leukemia.

All patients n=44				
Low risk n=16	High risk n=28			
ATRA or ATO in induction				
	ATRA+ATO + chemotherapy (%)	14 (31,8)	6 (37,5)	8 (28,5)
	ATRA + chemotherapy (%)	18 (40,9)	9 (56,2)	9 (32,1)
	ATO + chemotherapy (%)	3 (6,81)	0	3 (10,7)
	ATRA+ATO without chemotherapy (%)	9 (20,4)	1 (6,25)	8 (28,5)
	Initiated on day of diagnosis (%)	22 (50)	9 (56,2)	13 (46,4)
	Initiated > 1 day after diagnosis (%)	22 (50)	7 (43,7)	15 (53,5)
	Mean time in days to initiation of treatment (range)	2,5 (1-16)	2 (1-6)	2,7 (1-16)
Induction chemotherapy with ATRA and/or ATO				
	ARA-C+ anthracyclines (%)	2 (4,5)	1 (6,2)	1 (3,5)
	Anthracyclines only (%)	33 (75)	14 (87,5)	19 (67,8)

ARA-C: cytarabine; ATO: arsenic trioxide; ATRA: all-trans retinoic acid.

the high-risk and low-risk groups (60% vs. 40% [p=0.095]) but a difference was found in the rates of need for UTI at 30 days from diagnosis in the high-risk and low-risk groups (60.1% vs. 39.9% [p=0.011]). When comparing the mortality rates and need for UTI at 30 days from diagnosis in the treatment groups, ATRA+ATO without chemotherapy vs. the group that includes chemotherapy, no differences were found.

The low-risk group included 29 (60.4) patients, with an mean age of 39.4 years, 6 patients died early (2 due to hemorrhage and 4 due to infections), the average day to start treatment was 2.7 days and the average number of days of diagnostic opportunity was 14.6 days. The high-risk group included 19 (39.5%) patients, with an mean age of 40 years, 8 patients died early (4 due to hemorrhage and 4 due to infections), the average day to start treatment was 2 days and the average number of days of diagnostic opportunity was 14.2 days.

Among the 44 patients who received induction treatment, 9 (20.4%) of them had differentiation syndrome (DS); 3 (6.25%) patients died during the consolidation phase due to sepsis, and 2 patients after induction treatment decided to abandon treatment by their own will, the latter was still alive until the cut-off date of the study (64 and 78 months of survival) and in hematological remission. At the end of the study follow-up period, 23 (47.9%) patients had died.

Efficacy

In 26 patients, the molecular response after treatment was evaluated, all of which were negative for t (15; 17) (q22;-q12);(PML::RARA) and were classified as complete molecular response, in 2 patients the molecular response was not evaluated at the end of consolidation. Only 1 (3.5%) patient presented relapse of disease, having a CNS isolated relapse, this patient at the debut had been classified as low risk.

The median follow-up was 35.5 months. The median OS was not reached with a 5-year OS rate of 51.2% (95% CI, 38.6% to 67.9%) (Figure 1).

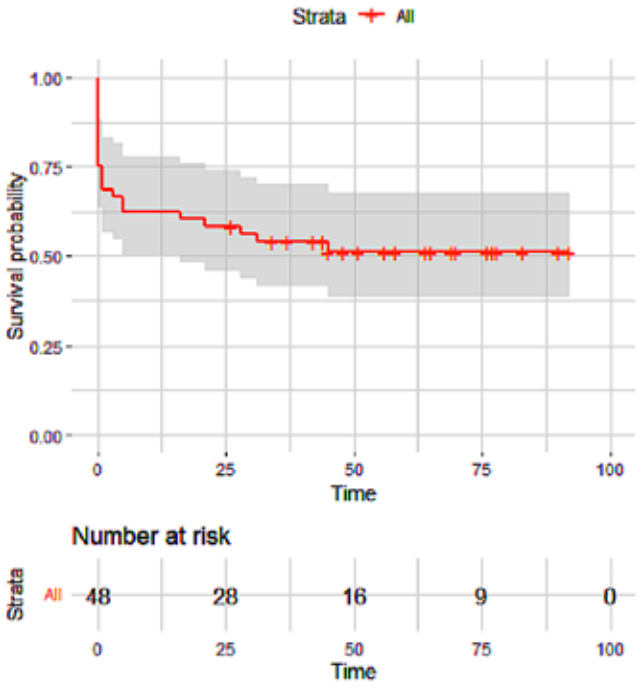

Figure 1. Kaplan Meier curve, showing overall survival for all patients included in the analysis. The time was recorded in months.

The 5-year OS according to the risk stratification of the disease (NCCN), in high risk and low risk there was no statistically significant difference 42.1% (95% CI, 24.9% to 71.3%) versus 57.3% (95%CI, 41.5% to 79.2%), respectively (p=0.19), the median OS in the high-risk group was 5 months (interquartile range 1-62 months), 9 patients (47.5%) were alive at that time. Median OS could not be achieved in the low-risk group (Figure 2).

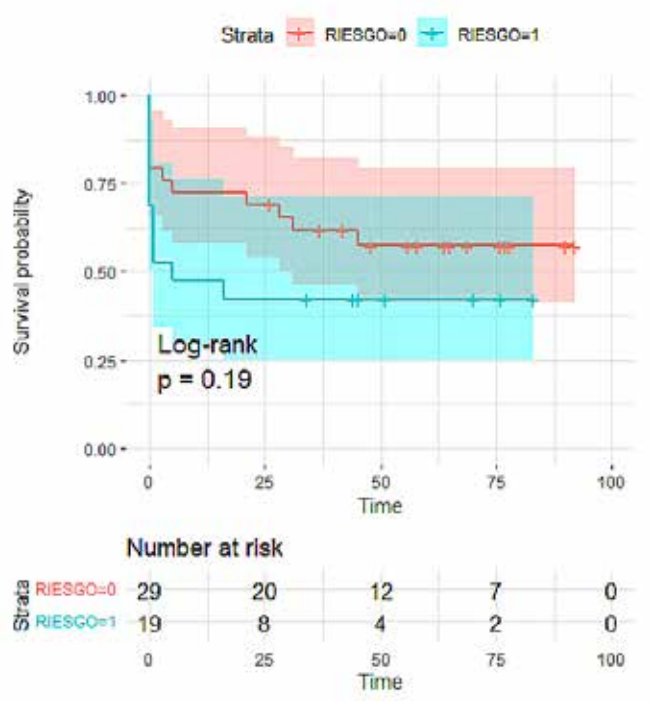

Figure 2. Kaplan Meier curve, which shows overall survival classifying patients according to risk, high and low groups (coded high = 1 and low = 0). The time was recorded in months.

The univariate analysis of other variables for OS is detailed in table 3.

Table 3. Univariate analysis of clinical variables of patients diagnosed with acute promyelocytic leukemia and its association with overall five-year survival.

Variable	n (%)	5-year survival (95% CI)	p* value
Sex			
Female	17 (35,4)	50% (35%-72%)	p=0,906
Male	31 (64,6)	53% (34%-83%)	
Start of ATRA or ATO on the day of diagnosis			p=0,658
Yes	22(50)	54% (36%-80%)	
No	22(50)	59% (42%-84%)	
Risk Group			p=0,118
Low	29(60,4)	57% (41%-79%)	
High	19(39,5)	42% (25%-71%)	
DIC			p=0,870
Yes	15(31,9)	48% (32%-70%)	
No	32(68,1)	60% (40%-91%)	

***Long Rank Test**
ATRA: All trans retinoic acid; ATO: arsenic trioxide. DIC: disseminated intravascular coagulation.

In the multivariate analysis, only age was identified as a significant adverse prognostic factor for OS, HR 1.05 (95% CI 1.02-1.08); with respect to fibrinogen level, days of diagnostic opportunity, sex, the onset of ATRA/ATO on the day of diagnosis, and risk group, there was no significant association found for OS (Table 4).

Table 4. Multivariate analysis for overall survival at five years in patients with Acute Promyelocytic Leukemia.

Variable	HR (IC 95%)	Value of p
Age (years)	1,05 (1,02-1,08)	p=0,002
Fibrinogen level mg/dl	1 (0,99-1.05)	p=0,675
Days of diagnostic opportunity	0,98 (0,929-1,04)	p=0,607
Sex		p=0,413
Male	Reference	
Female	1,51 (0,57-4,1)	
Start of ATRA/ATO on the day of diagnosis		p=0,725
No	Reference	
Yes	0,81 (0,24-2,74)	
Risk Group		p=0,339
Low	Reference	
High	0,63 (0,24-1,63)	

ATRA: All trans retinoic acid; ATO: arsenic trioxide. HR: Hazard Ratio.

DISCUSSION

Historically, in the USA the APL has been recognized as a rare acute myeloid leukemia subtype, that represents between 5 to 15 % of all cases of AML10. The Swedish Registry reported a lower percentage, about 3.4 % of all AML cases[11], meanwhile, there are reports in South America, Central America, and Spain that put APL as the most frequent subtype of AML among Hispanics, with rates between 22 to 38% of all cases of AML[12,13]. In the registry of our study, with the data of a reference center from Ecuador, it can be observed that PML is the most common subtype of AML with 16.4% of all cases, being slightly lower than other prevalence rates in other Hispanic countries. In Ecuador there exist many problems in the Health Care System that avoid those patients with leukemia arrive soon at the reference centers, and this may explain the lower rate of APL in this cohort, explained by a sub-diagnosis, given that patients with APL may be very ill (probably in worst condition than a patient with other subtypes of AML) and could die before even get the chance to be attended in a reference center or diagnosed properly. It must also be considered that for the same reasons explained previously there could exist a sub-diagnosis of other subtypes of AML provoking a false increase in the rate of APL.

The average age reported in Latin America for APL is lower (Brazil 36 years old[14], Mexico 37 years old[15], this studies were made in patients older than 15 years old) than the reported in Sweden (56 years old)[16] and the USA (average age was 48 years old, including pediatric patients)[17], in our cohort the average age is a little older with 41 years old (not including pediatric patients) but is close to that referred by other Latin American countries, there is also important to emphasize that no indigenous patients with APL where found in this cohort (defined as patients who spoke an ancient language), all the patients in this study where mixed race except for one that was Afro-Ecuadorian, this patient presented APL secondary to previous chemotherapy. This patient with secondary APL represented the 2.1 %, being lower than the 5-22% reported in other studies regarding secondary APL[18-20].

The Swedish LPA registry revealed a mortality rate of 25% in the first 30 days of treatment, with no improvement between 1997 and 2008 compared to 2009 and 2013[16], in the Brazilian registry published by Silva et al[14], reaches an early mortality of 29%, while the registry of Zapata et al[15] in Mexico, reports 13.9% and that of Park et al[17] in the US reaches 17%. These figures vary depending on the registration center and its realities, but they are still high. In our case is as high as 31.2%. We consider that the high rate of early mortality that we report, is given in first place by the already known coagulopathy associated with this disease (31.9% developed DIC, a figure like that found in other studies) that represented 40% of early deaths, this cause of early death perhaps is influenced in our cohort by the delay of diagnosis and treatment. Given that on average patients took 14 days from the onset of symptoms to their diagnosis, adding to this the delay in initiation of ATRA (2.5 days on average) given by the irregular availability of ATRA in our center.

The rate of early death from infections is unacceptably high (16.6%), it was possible to isolate MDR bacteria in the cultures of 83% of patients that died from sepsis, perhaps it is possible that this high rate of MDR bacteria could be a modifiable factor if it is implemented an adequate infection control program, and thus reduce the high rate of early mortality.

The reported rates of DS are highly variable between 2-48%[21-23], in our cohort, it was present in 20.4% of cases, we believe that there may be an underdiagnose of DS, given the limitations of collecting data retrospectively. No isolated cases of DS could be observed as a cause of early death, given that patients who developed DS and died had associated sepsis or bleeding.

The rates of high-risk APL in different real-life reports range from 24-52%[14,16,24,25] like that reported in our center, which was 39.5%. We believe that the reason why no difference in OS could be found between the high and low risk group of APL patients is due to the limitations of the small sample size of this analysis.

The study by Pagoni et al.,[25] (Greece and Cyprus, 2011), Lee et al.,[26] (South Korea, 2015), Silva et al.,14 (Brazil year 2018) Steffenello-Durigon et al., [27] (Brazil year 2021), reported a 5-year OS of 78.4%; 60.8%; 59.2% and 82.7% respectively, these OS rates are directly influenced by the early mortality rate. In general, OS in APL in the world is more frequently influenced by the rate of early fatal hemorrhages, since they are the most common cause of death in LPA, as shown in the Greek-Cypriot study[25], the Korean study[26] and the Brazilian study by Steffenello-Durigon et al.27 In the Brazilian study by Silva et al.,[14] to the already high rate of fatal bleeding must be added a high rate of infections related to induction chemotherapy, similar to what was observed in our study. To the point that in these two registries the most frequent cause of early death was not fatal hemorrhages but infections and thus justifying why our registry presents a 5-year OS (51.3%) even lower than other real-world studies. It is interesting to note that the patients in the report by Silva et al.,[14], received more intensive induction chemotherapy (7 + 3 with ATRA) than our cohort, that generally received AIDA-2000 scheme that we considered less intensive as induction treatment for LPA.

Age was the only significant adverse prognostic factor, underscored by the significant difference in mean age between patients who died early and those who did not (52.3 vs 34.3 respectively) in this cohort. Marking that greater vulnerability of patients to coagulopathy and treatment-related infections in dependence on age.

In our registry there were two young patients who only received induction treatment with AIDA-2000 scheme and then abandoned the treatment, but despite this they have achieved prolonged survival (more than 60 months) without hematological relapse. This marks perhaps the interesting possibility of being able to identify in the future, patients who could require less intensive treatment, with perhaps the same good results.

CONCLUSIONS

There are few reports regarding clinical outcomes in leukemias in Ecuador, this real-world study being the first of its kind in Ecuador showing a survival analysis on LPA. However, we suggest that more studies with the collaboration of local centers must be conducted with the creation of a National Registry of Leukemias that is still lacking in our country.

The poor results of OS in this cohort have an explanation in the problems of the National Health System such as limited access and low budget for health, which generates an important delay in the reference of patients to specialized centers, and also a lack of indispensable medication (like ATRA) for the management of oncologic diseases

Finally, It is essential the implementation of National Programs that implies awareness of APL in primary care professionals and urgency care professionals of the country, by this enhancing the medical attention provided to a disease considered as a hematological urgency but which has a potential good prognosis with prompt and adequate treatment.

ABBREVIATIONS:

AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; ATO: arsenic trioxide; ATRA: all trans retinoic acid; CR: complete response; DIC: disseminated intravascular coagulation; DS: differentiation syndrome; ED: early death; EFS: event-free

survival; FAB: French-American-British; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; HECAM: Hospital de Especialidades Carlos Andrade Marín; IC-APL: International Consortium on Acute Promyelocytic Leukemia; MDR: multidrug-resistant; NCCN: National Comprehensive Cancer Network; OS: the overall survivaland; PETHEMA: Programa Español de Tratamientos en Hematología; RT-PCR: reverse transcriptase polymerase chain reaction; TTD: Time-to-diagnosis

AUTHORS' CONTRIBUTION

OA: Conception and design of the work; Collection/obtaining, analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript; Approval of its final version, Accountability. (ICMJE). ML: Conception, research design; Data collection; Approval of final version, Accountability (ICMJE). LS, PV: Manuscript drafting; Critical revision of the manuscript; Analysis and interpretation of data; Approval of the final version, Accountability. (ICMJE). DG, JC: Drafting of the manuscript; Critical revision of the manuscript. Approval of the final version, Accountability (ICMJE). RM: Data collection; Approval of final version, Accountability (ICMJE).

AVAILABILITY OF DATA AND MATERIALS

Bibliographic resources of free and limited use were used. The information collected is available upon request to the main author.

ETHICS COMMITTEE APPROVAL AND CONSENT TO PARTICIPATE IN THE STUDY.

The scientific article was approved by peers and by the Human Research Ethics Committee - CEISH/ HECAM.

CONSENT FOR PUBLICATION

The publication was approved by the Human Research Ethics Committee of HECAM in Act 002 dated 2023-04-07.

FINANCING

The work was financed by the authors' own resources.

CONFLICTS OF INTEREST

The authors reported having no personal, financial, intellectual, economic or corporate conflicts of interest.

BIBLIOGRAPHIC REFERENCES

1. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia [Internet]. 2022 Jul 1 [cited 2022 Dec 4];36(7):1703–19. Available from: https://pubmed.ncbi.nlm.nih.gov/35732831/

2. Mejía-Buriticá L, Torres-Hernández JD, Vásquez G de J. Leucemia promielocítica aguda. Estado del arte. Iatreia [Internet]. 2021 Sep 8 [cited 2022 Dec 1];34(1):42–53. Available from: https://revistas.udea.edu.co/index.php/iatreia/article/view/342244

3. Li G, Wu J, Li R, Pan Y, Ma W, Xu J, et al. Improvement of Early Death in Acute Promyelocytic Leukemia: A Population-Based Analysis. Clin Lymphoma Myeloma Leuk [Internet]. 2022 Nov 28 [cited 2022 Dec 1]; Available from: https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(22)01734-7/fulltext

4. Tallman MS, Altman JK. Curative Strategies in Acute Promyelocytic Leukemia. Hematology [Internet]. 2008 Jan 1 [cited 2022 Dec 1]; (1):391–9. Available from: https://ashpublications.org/hematology/article/2008/1/391/95862/Curative-Strategies-in-Acute-Promyelocytic

5. Garrido D, Granja M. Limitaciones en el manejo de Mieloma Múltiple en Ecuador. Rev la Fac Ciencias Médicas [Internet]. 2019 Dec 11 [cited 2023 Jan 23];44(2):5–9. Available from: https://revistadigital.uce.edu.ec/index.php/CIENCIAS_MEDICAS/article/view/2686

6. Adès L, Sanz MA, Chevret S, Montesinos P, Chevallier P, Raffoux E, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): a comparison of French-Belgian-Swiss and PETHEMA results. Blood [Internet]. 2008 Feb 1 [cited 2022 Dec 1];111(3):1078–84. Available from: https://ashpublications.org/blood/article/111/3/1078/25533/Treatment-of-newly-diagnosed-acute-promyelocytic

7. Lo-Coco F, Avvisati G, Vignetti M, Breccia M, Gallo E, Rambaldi A, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood [Internet]. 2010 Oct 28 [cited 2022 Dec 1];116(17):3171–9. Available from: https://ashpublications.org/blood/article/116/17/3171/27969/Front-line-treatment-of-acute-promyelocytic

8. Corrêa de Araujo Koury L, Ganser A, Berliner N, Rego EM. Treating acute promyelocytic leukaemia in Latin America: lessons from the International Consortium on Acute Leukaemia experience. Br J Haematol. 2017;177(6):979–83. Available from: https://pubmed.ncbi.nlm.nih.gov/28466545/

9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Acute Myeloid Leukemia Version 2.2022. junio 14, 2022. Disponible en: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1411

10. Tallman MS, Altman JK. Curative Strategies in Acute Promyelocytic Leukemia. Hematology [Internet]. 2008 Jan 1 [cited 2022 Dec 1];2008(1):391–9. Available from: https://ashpublications.org/hematology/article/2008/1/391/95862/Curative-Strategies-in-Acute-Promyelocytic

11. Juliusson G, Lazarevic V, Hörstedt AS, Hagberg O, Höglund M. Acute myeloid leukemia in the real world: Why population-based registries are needed. Blood. 2012;119(17):3890–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22383796/

12. Matasar MJ, Ritchie EK, Consedine N, Magai C, Neugut AI. Incidence rates of acute promyelocytic leukemia among Hispanics, blacks, Asians, and non-Hispanic whites in the United States. Eur J Cancer Prev [Internet]. 2006 Aug [cited 2022 Dec 2];15(4):367–70. Available from: https://pubmed.ncbi.nlm.nih.gov/16835508/

13. Dan Douer; Acute promyelocytic leukemia in Latino populations. Cancer Epidemiol Biomarkers Prev 1 November 2007; 16, 11_Supplement: CN02–02. Available from: https://aacrjournals.org/cebp/article/16/11_Supplement/CN02-02/174810/Acute-promyelocytic-leukemia-in-Latino-populations

14. Silva WF d., Rosa LI da, Marquez GL, Bassolli L, Tu

cunduva L, Silveira DRA, et al. Real-life Outcomes on Acute Promyelocytic Leukemia in Brazil – Early Deaths Are Still a Problem. Clin Lymphoma, Myeloma Leuk [Internet]. 2019;19(2):e116–22. Available from: https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(18)31311-9/fulltext

15. Zapata-Canto N, Aguilar M, Arana L, Montano E, Ramos-Penafiel C, Pena JAD la, et al. Acute Promyelocytic Leukemia: A Long-Term Retrospective Study in Mexico. J Hematol [Internet]. 2021 Apr [cited 2022 Dec 2];10(2):53-63. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8110230/

16. Lehmann S, Deneberg S, Antunovic P, Rangert-Derolf, Garelius H, Lazarevic V, et al. Early death rates remain high in high-risk APL: update from the Swedish Acute Leukemia Registry 1997-2013. Leukemia [Internet]. 2017 Jun 31 [cited 2022 Nov 16];31(6):1457–9. Available from: https://pubmed.ncbi.nlm.nih.gov/28232742/

17. Chen Y, Kantarjian H, Wang H, Cortes J, Ravandi F. Acute promyelocytic leukemia: a population-based study on incidence and survival in the United States, 1975-2008. Cancer [Internet]. 2012 Dec 1 [cited 2022 Nov 16];118(23):5811–8. Available from: https://pubmed.ncbi.nlm.nih.gov/22707337/

18. Braun T, Cereja S, Chevret S, Raffoux E, Beaumont M, Detourmignies L, et al. Evolving characteristics and outcome of secondary acute promyelocytic leukemia (APL): A prospective analysis by the French-Belgian-Swiss APL group. Cancer. 2015;121(14):2393–9. Pollicardo N, O'Brien S, Estey EH, Al-Bitar M, Pierce S, Keating M, et al. Secondary acute promyelocytic leukemia. Characteristics and prognosis of 14 patients from a single institution. Leukemia [Internet]. 1996 Jan 1 [cited 2022 Nov 16];10(1):27–31. Available from: https://europepmc.org/article/med/8558933;

19. Jantunen E, Heinonen K, Mahlamäki E, Penttilä K, Kuittinen T, Lehtonen P, et al. Secondary acute promyelocytic leukemia: an increasingly common entity. Leuk Lymphoma [Internet]. 2007 Jan [cited 2022 Nov 16];48(1):190–1. Available from: https://pubmed.ncbi.nlm.nih.gov/17325866/

20. Montesinos P, Bergua JM, Vellenga E, Rayón C, Parody R, De La Serna J, et al. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. Blood [Internet]. 2009 Jan 22 [cited 2022 Nov 17];113(4):775–83. Available from: https://pubmed.ncbi.nlm.nih.gov/18945964/

21. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A, et al. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. Blood. 2000;95(1):90–5. Available from: https://pubmed.ncbi.nlm.nih.gov/10607690/

22. De Botton S, Dombret H, Sanz M, Miguel JS, Caillot D, Zittoun R, et al. Incidence, Clinical Features, and Outcome of AllTrans-Retinoic Acid Syndrome in 413 Cases of Newly Diagnosed Acute Promyelocytic Leukemia. Blood. 1998 Oct 15;92(8):2712–8. Available from: https://pubmed.ncbi.nlm.nih.gov/9763554/

23. Hassan IB, Zaabi MRA, Alam A, Hashim MJ, Tallman MS, Kristensen J. Characteristics features and factors influencing early death in Acute promyelocytic leukemia; Experience from United Arab Emirates (UAE). Int J Hematol [Internet]. 2017 Jul 1 [cited 2022 Nov 17];106(1):90–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28293819/

24. Pagoni M, Garofalaki M, Panitsas F, Manola K, Psarra K, Economopoulos P, et al. Acute Promyelocytic Leukemia: an Experience on 95 Greek Patients Treated in the All-Trans-Retinoic Acid Era. Mediterr J Hematol Infect Dis [Internet]. 2011 [cited 2022 Nov 17];3(1):1–15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248330/

25. Lee HJ, Kim DH, Lee S, Koh MS, Kim SY, Lee JH, et al. Analysis of factors affecting hemorrhagic diathesis and overall survival in patients with acute promyelocytic leukemia. Korean J Intern Med [Internet]. 2015 Nov 1 [cited 2022 Nov 17];30(6):884–90. Available from: https://pubmed.ncbi.nlm.nih.gov/26552464/

26. Lee HJ, Kim DH, Lee S, Koh MS, Kim SY, Lee JH, et al. Analysis of factors affecting hemorrhagic diathesis and overall survival in patients with acute promyelocytic leukemia. Korean J Intern Med [Internet]. 2015 Nov 1 [cited 2022 Dec 2];30(6):884-90. Available from: https://pubmed.ncbi.nlm.nih.gov/26552464/

27. Steffenello-Durigon G, Bigolin A, Moraes ACR de, Rudolf-Oliveira RC, Moral JAG Del, Santos-Silva MC. Follow-up and outcome of the twelve-year experience in adult patients with acute promyelocytic leukemia. Hematol Transfus Cell Ther [Internet]. 2021 Mar 26 [cited 2022 Dec 2];43(1):21–7. Available from: http://www.scielo.br/j/htct/a/nGRtYSthYvKQXDVcML88BNw/?lang=en&format=html