



Results of the implementation of the PETHEMA LPA 99 protocol for treating children with acute promyelocytic leukemia in Bogotá, Colombia

Resultados de la implementación del protocolo PETHEMA LPA 99 en el tratamiento de niños con leucemia promielocítica aguda en Bogotá, Colombia

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Abstract

Introduction: In the United States, between 4 and 8% of children with acute myeloid leukemia have acute promyelocytic leukemia (APL), but a higher incidence of this malignancy has been reported in Latin America (20%-28%). The implementation of the PETHEMA LPA 99 protocol, designed for the treatment of APL in adults, has shown an overall survival (OS) >80%.

Objective: To describe the results obtained after the implementation of the PETHEMA LPA 99 protocol to treat children with APL at the Fundación Hospital Pediátrico La Misericordia in Bogotá, D.C., Colombia.

Materials and methods: Descriptive and retrospective cohort study. The medical records of 30 pediatric patients (<18 years) with APL, who were treated using the PETHEMA LPA 99 protocol between January 2005 and December 2012, were reviewed. Data on the following variables were obtained: early death, death during induction therapy, OS, event-free survival (EFS), and relapse.

Results: The male sex was predominant (60%) among the 30 patients included in the study. Regarding risk classification, 13 (43%) were classified as high-risk patients, 12 (40%) as medium-risk, and 5 (17%) as low-risk. Seven individuals died: 2 before receiving cancer treatment, 2 during induction therapy, and 3 after relapse. Relapse was reported in 5 patients. There were no deaths during the consolidation or maintenance phases. OS was 75.4% (95%CI: 55.1-87.5) and EFS was 64.3% (95%CI: 40-80.5). Moreover, OS at 11 years was 80%, 91.7%, and 59.2% for low-risk, intermediate-risk, and high-risk patients, respectively. The median follow-up time was 6.35 years (0-11.43 years).

Conclusions: In general, the implementation of the PETHEMA LPA 99 protocol to treat APL in the study population showed very satisfactory results. Therefore, its use in pediatric population is recommended, taking into account the adjustments described in the protocol regarding the characteristics of this age group.

Keywords: Acute Promyelocytic Leukemia; Children; Survival; Treatment (MeSH).

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Resumen

Introducción. En Estados Unidos de América, entre 4 y 8% de niños con leucemias mieloides agudas tienen leucemia promielocítica aguda (LPA), mientras que en Latinoamérica se ha descrito una mayor incidencia de esta neoplasia (20-28%). La implementación del protocolo PETHEMA LPA 99, diseñado para el tratamiento de LPA en adultos, ha mostrado una supervivencia global (SG) >80%.

Objetivo. Describir los resultados de la aplicación del protocolo PETHEMA LPA 99 en el tratamiento de niños con LPA en la Fundación Hospital Pediátrico la Misericordia, en Bogotá D.C., Colombia.

Materiales y métodos. Estudio de cohorte descriptivo y retrospectivo. Se revisaron las historias clínicas de 30 pacientes pediátricos (<18 años) con LPA que recibieron tratamiento mediante el protocolo PETHEMA LPA 99 entre enero de 2005 y diciembre de 2012. Se obtuvieron datos sobre las siguientes variables: muerte temprana, muerte en terapia de inducción, SG, supervivencia libre de evento (SLE) y recaída.

Resultados. De los 30 pacientes, la mayoría eran de sexo masculino (60%). Respecto a la clasificación de riesgo, 13 (43%) fueron clasificados como pacientes de riesgo alto; 12 (40%), de riesgo intermedio, y 5 (17%), de riesgo bajo. 7 individuos murieron: 2 antes del tratamiento oncológico, 2 durante la terapia de inducción y 3 luego de presentar recaída. Se reportó recaída en 5 pacientes. No hubo muertes durante las fases de consolidación o de mantenimiento. La SG fue de 75.4% (IC95%: 55.1-87.5) y la SLE fue de 64.3% (IC95%: 40-80.5). La SG a 11 años fue de 80%, 91.7% y 59.2% para los pacientes de riesgo bajo, riesgo intermedio y riesgo alto, respectivamente. La mediana de seguimiento fue 6.35 años (0-11.43 años).

Conclusiones. En general, la implementación del protocolo PETHEMA LPA 99 en el tratamiento de la LPA en la población de estudio mostró resultados muy satisfactorios, por lo que se recomienda su uso en población pediátrica, teniendo en cuenta los ajustes recomendados por el protocolo en relación con las características de este grupo etario.

Palabras clave: Leucemia promielocítica aguda; Niños; Supervivencia; Tratamiento (DeCS).

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Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) with unique morphological, cytogenetic, and molecular characteristics. In the United States, 4–8% of children with AML have APL,¹ and in Latin America, a higher incidence has been reported in Brazil (28%),² Mexico (20%), and Venezuela and Peru (22% each).^{1–3}

APL is characterized by a reciprocal translocation between the *PML* gene on chromosome 15 and the retinoic acid receptor alpha on chromosome 17, which forms the PML-RAR α protein.^{1,2} This translocation —t(15;17)— is found in 95% of cases of this type of leukemia; however, APL can also be caused by other translocation variants such as t(5;17) and t(11;17) that cause 5% of cases and have similar pathophysiological effects.^{2,4}

Severe coagulopathy and bleeding are the main complications of APL, which are more common in the microgranular variant (M3v). Since 1980, with the discovery of all-trans retinoic acid (ATRA) —a drug that induces the differentiation of promyelocytes into mature granulocytes—, a new era in the treatment of this disease began, in which a marked increase in both overall survival (OS) and event-free survival (EFS) has been achieved.¹

The PETHEMA LPA 99 protocol was developed by the Spanish Society of Hematology and Hemotherapy within the framework of the Spanish Program for the Treatment of Malignant Hemopathies to treat APL. It has shown favorable EFS and OS rates with acceptable toxicity in the induction, consolidation, and maintenance phases in adult patients. This protocol has criteria for the classification of disease risk and uses ATRA in all phases of treatment: combined with anthracyclines during induction-consolidation, and with mercaptopurine and methotrexate during maintenance until completing 2 years of treatment. The implementation of this strategy has achieved an OS >80%.

Countries such as Spain, Netherlands, Belgium, Czech Republic, Japan, Korea, Turkey, Tunisia, Argentina, Brazil, Chile, Mexico and Uruguay have achieved good survival results with the implementation of the PETHEMA LPA 99 protocol, as reported in the literature.^{5–12} In Colombia, in 2011, an evidence-based clinical practice guideline for the care of children with APL was developed, which included the same drugs that are recommended in the protocol as treatment drugs.¹³

The main objective of the present study was to describe the results of the PETHEMA LPA 99 protocol implementation in the treatment of children with APL at the Fundación Hospital Pediátrico La Misericordia, located in Bogotá D.C., Colombia.

Materials and methods

A descriptive and retrospective cohort study was conducted. The medical records of 30 pediatric patients (under 18 years of age) with APL who received treatment based on the PETHEMA LPA 99 protocol at the Fundación Hospital Pediátrico La Misericordia between January 2005 and December 2012 were reviewed. Data on the following variables were obtained: early death, death during induction therapy, OS, EFS and relapse.

For the selection of participants, inclusion criteria were being under the age of 18; having a diagnosis of *de novo* morphologic APL corresponding to subtype M3 or m3v with immunophenotyping by flow cytometry

compatible with APL; presentation of t(15;17) translocation; having a diagnosis of atypical morphology APL but with t(15;17) translocation positive by RT-PCR; being on treatment based on the PETHEMA LPA 99 protocol since the induction phase in the hospital; having a normal echocardiogram result; and having the informed consent signed by the parents accepting the treatment.

Patients who did not have a report of t(15;17), due to unavailability of the test in the institution or to failures in test performance, were included in the protocol based on myelogram morphology and positivity of immunophenotyping by flow cytometry.

Patients diagnosed with AML other than APL, or who had received cancer treatment at another institution prior to admission to the Fundación Hospital Pediátrico La Misericordia were excluded.

Treatment

Participants received treatments based on the PETHEMA LPA 99 protocol and according to their classification in the risk group, which included transfusion support management with platelets to maintain blood counts >30x10⁹/L, cryoprecipitates to maintain fibrinogen above 100 mg/dL, and fresh frozen plasma to maintain clotting times less than twice the normal value. The protocol is described in Table 1.

Table 1. Institutional protocol for the treatment of acute promyelocytic leukemia based on the PETHEMA LPA protocol 99.

Remission induction		
Idarubicin		12 mg/m ² /day (days 2, 4, 6 and 8)
ATRA		25 mg/m ² /day (from day 1 until complete remission)
Prednisolone		0.5 mg/kg/d (days 1-15)
Consolidation (21-day cycles)		
Low risk	Idarubicin	5 mg/m ² /day (days 1-4) + ATRA at a dose of 25 mg/m ² /day (15 days)
	Mitoxantrone	10 mg/m ² /day (days 1-5) + ATRA at a dose of 25 mg/m ² /day (15 days)
	Idarubicin	12 mg/m ² /day (day 1) + ATRA at a dose of 25 mg/m ² /day (15 days)
Medium and high risk	Idarubicin	7 mg/m ² /day (days 1-4) + ATRA at a dose of 25 mg/m ² /day (15 days)
	Mitoxantrone	10 mg/m ² /day (days 1-5) + ATRA at a dose of 25 mg/m ² /day (15 days)
	Idarubicin	12 mg/m ² /day (days 1 and 2) + ATRA at a dose of 25 mg/m ² /day (15 days)
Maintenance (begins one month after consolidation and ends two years later)		
ATRA		25 mg/m ² /day (15 days every 3 months for 6 cycles)
Methotrexate		15 mg/m ² /day each week
6-mercaptopurine		50 mg/m ² /day

ATRA: All-trans retinoic acid.

Source: Own elaboration.

Definitions

Risk classification

Low risk: patient with white blood cell count $<10\,000/L$ and platelets $>40 \times 10^9/L$ at diagnosis.

Medium risk: patient with white blood cell count $<10\,000/L$ and platelets $<40 \times 10^9/L$ at diagnosis.

High risk: patient with white blood cell count $>10\,000/L$ at diagnosis.

Morphologic complete remission

This remission is defined as the absence of extramedullary leukemic infiltration accompanied by a hemogram with neutrophil counts $>1.5 \times 10^9/L$ and platelets counts $>100 \times 10^9/L$, absence of atypical blasts or promyelocytes and a normocellular bone marrow aspirate with less than 5% blasts or atypical promyelocytes. The treatment protocol specifies a maximum time limit of 90 days from the start of ATRA treatment to achieve the aforementioned criteria.

Events

Death during induction: death occurring between the day induction treatment is started and before remission is documented at the end of induction treatment.

Death during treatment: death occurring between the first day of treatment until the end of treatment.

Relapse: having more than 20% of atypical blasts/promyelocytes in 1 bone marrow aspirate after entering remission, having more than 5% of atypical blasts/promyelocytes in 2 bone marrow examinations 1 week apart, or having the *PML-RAR α* gene reappear in 2 consecutive bone marrow samples analyzed by RT-PCR at any time after the end of the consolidation phase.

Outcomes

Overall survival: time from diagnosis until death from any cause or until the last time the subject was known to be alive.

Event-free survival: time elapsed between initiation of treatment and early death, death during induction, disease relapse, development of second malignancy, or death due to toxicity; in patients who are alive and in remission, this moment will be the date of the last time the subject was known to be alive.

Statistical analysis

Qualitative variables were analyzed using frequencies and percentages, whereas quantitative variables were analyzed using averages, medians, and dispersion measures such as interquartile range, minimum value and maximum value. The Kaplan-Meier method and the log-rank test were used for survival analysis.

Ethical considerations

The ethical principles for medical research involving human beings established by the Declaration of Helsinki¹⁴ and the provisions on health research in Resolution 8430 of 1993 of the Ministry of Health of Colombia were

followed.¹⁵ The present study is considered a risk-free research as no intervention was performed on the patients and only the information available in their medical records was analyzed. This research was endorsed by the Ethics Committee of the Fundación Hospital Pediátrico de La Misericordia through Minutes CEI 006-17 of May 17, 2017. In addition, the confidentiality of patients' personal data was ensured by re-identifying their medical records.

Results

30 patients with a median age of 10 years were analyzed (range: 1-16 years); the majority were males (60%) and lived in Bogotá at the time of diagnosis (67%) (Figure 1).

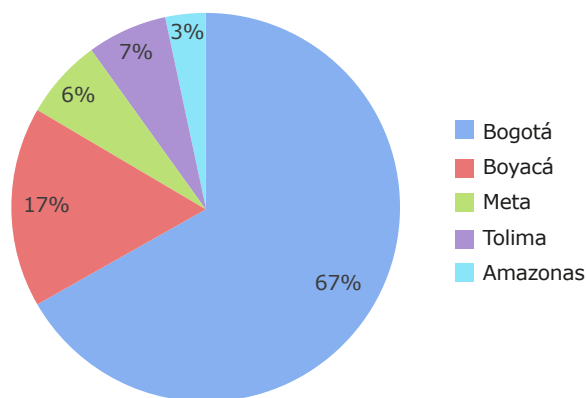


Figure 1. Place of residence of participants. Source: Own elaboration.

Laboratory test findings at diagnosis in the patients analyzed are described in Table 2.

Table 2. Blood count findings at diagnosis.

Test	Median	Range (max-min)	Interquartile range
Hemoglobin	8.65	4.6-13.7	3.18
Leukocytes	6 045	1 200-350 000	24 617
Platelets	33 000	6 000-454 000	49 750

Source: Own elaboration.

The diagnosis of APL was made by morphology and flow cytometry in all cases, the immunophenotyping by flow cytometry being characteristic in 100% of the sample (Table 3).

Table 3. Phenotyping by flow cytometry at diagnosis

Positive markers	n	%
Myeloperoxidase	30	100
CD 13	28	93
CD 33	30	100
CD 117	28	93
CD 38	14	47
CD 64	21	70
CD 45	6	20
CD 34	1	3

Source: Own elaboration.

Translocation, which was established by RT-PCR, was positive for t(15;17) in 18 patients (60%) and negative in 1 (3.33%); no data were obtained in 11 cases (37%) due to unavailability of the test in the institution or failure in the performance of the test. The patient with a negative result was treated with the PETHEMA LPA 99 protocol and was included in the analysis due to their cell morphology and typical clinical characteristics of APL.

The 5 (16.66%) patients with m3v variant were classified as high risk; of these, 3 died and 2 were alive at the time of the present research.

Relapses

Five patients relapsed, four with isolated involvement in bone marrow and one with both bone marrow and central nervous system involvement. Three of the patients who relapsed died and two were alive at the time of this study. Both survivors had isolated hematologic relapse with classic morphology, one was classified as high risk 1.5 years after diagnosis, and the other was medium-risk 3.5 years after diagnosis. These two patients achieved second remission with arsenic trioxide and received consolidation treatment with autologous hematopoietic progenitor cell transplantation.

Mortality

Of the 7 patients who died, 2 died within the first 24 hours of hospital admission, one from intracranial hemorrhage and one from leukostasis; neither was able to receive chemotherapy. Another patient was admitted with a massive intracranial hemorrhage and given supportive therapy; nevertheless, he died after 7 days and was unable to undergo chemotherapy due to his clinical condition. A fourth patient received chemotherapy according to the protocol but had severe epistaxis and intracranial hemorrhage and died after 12 days. Finally, 3 patients died after relapse: 2 relapsed during maintenance and died 10 and 12 months after diagnosis; the other achieved second molecular remission with the PETHEMA LPA 99 treatment protocol for relapse and consolidation with autologous hematopoietic precursor cell transplantation but died after a second relapse 3 months after transplantation and 3.5 years after diagnosis. Table 4 describes the characteristics of the patients who died.

With regard to the social security scheme, 19 (63%) participants were from the contributory scheme and 11 (37%) from the subsidized scheme; no statistically significant differences were observed in OS between these two groups (Figure 2).

Table 4. Description of patients in the cohort who died.

Age and risk at admission - m3v morphology	Moment of death	Cause of death
1. Male - 2 years (high risk)	Within the first 24 hours	Severe ICH
2. Male - 15 years (high risk - microgranular)	Within the first 24 hours	Leukostasis (350 000 leukocytes at diagnosis)
3. Male 5 years (high risk)	At day 7	Massive ICH
4. Male - 15 years (medium risk)	At day 12	Severe ICH
5. Female - 9 years (high risk - microgranular)	At 10 months	She relapsed and died during maintenance
6. Male - 14 years (high risk - microgranular)	At 12 months	He relapsed and died during maintenance
7. Female - 10 years (low risk)	At 42 months	Second relapse 3 months after - hematopoietic progenitor cell transplantation

ICH: Intracranial hemorrhage.

Source: Own elaboration.

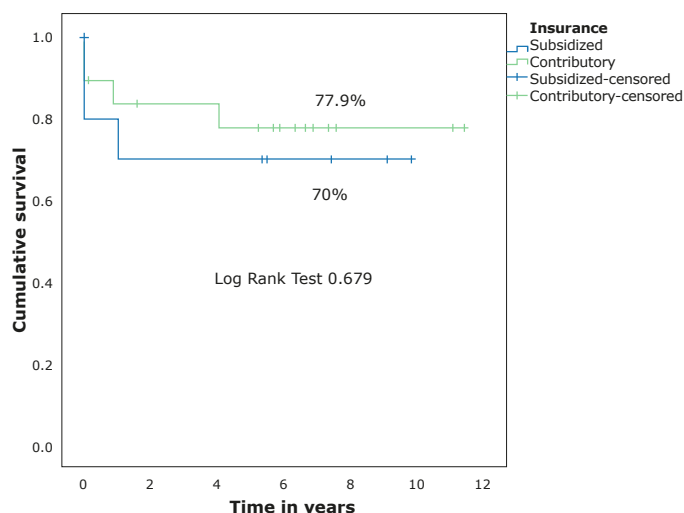


Figure 2. Survival according to the social security scheme of the participants.

Source: Own elaboration.

Concerning risk classification, 13 (43%) participants were classified as high risk, 12 (40%) as medium risk, and 5 (17%) as low risk. The 11-year OS, according to risk, was 59.2%, 91.7% and 80% for high-, medium- and low-risk patients,

respectively (Figure 3). OS for all participants was 75.4% (95%CI: 55.1-87.5) (Figure 4), while EFS was 64.3% (95%CI: 40-80.5) with a median follow-up time of 6.35 years (0-11.43 years) (Figure 5).

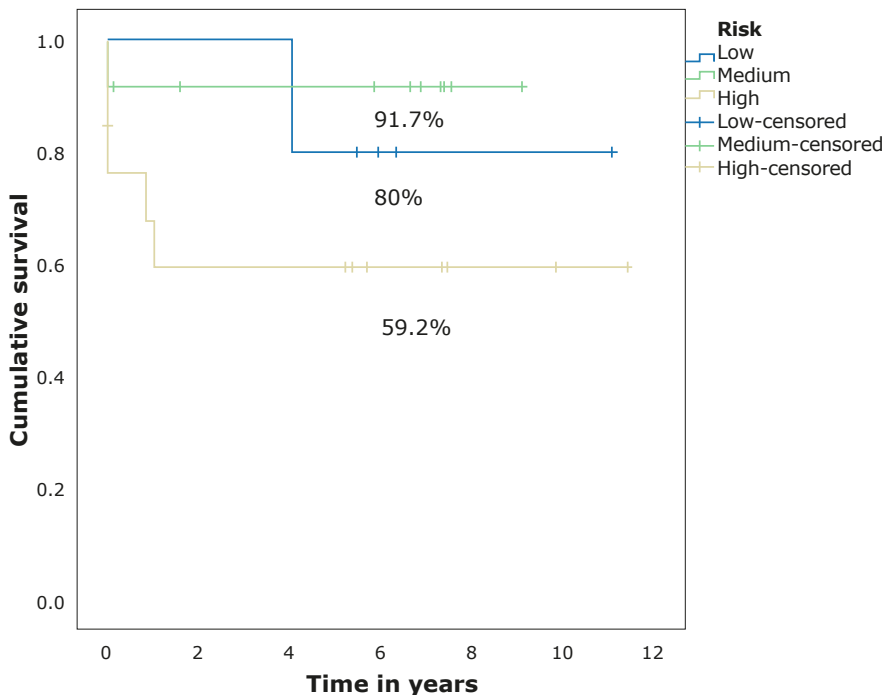


Figure 3. Survival according to risk classification of participants. Source: Own elaboration.

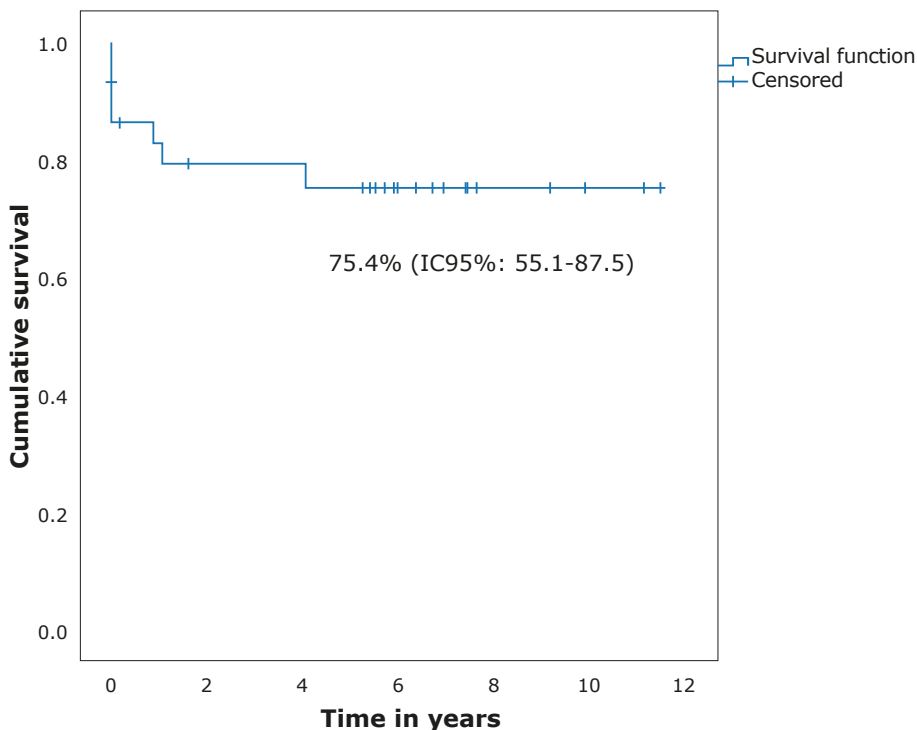


Figure 4. Overall survival. Source: Own elaboration.

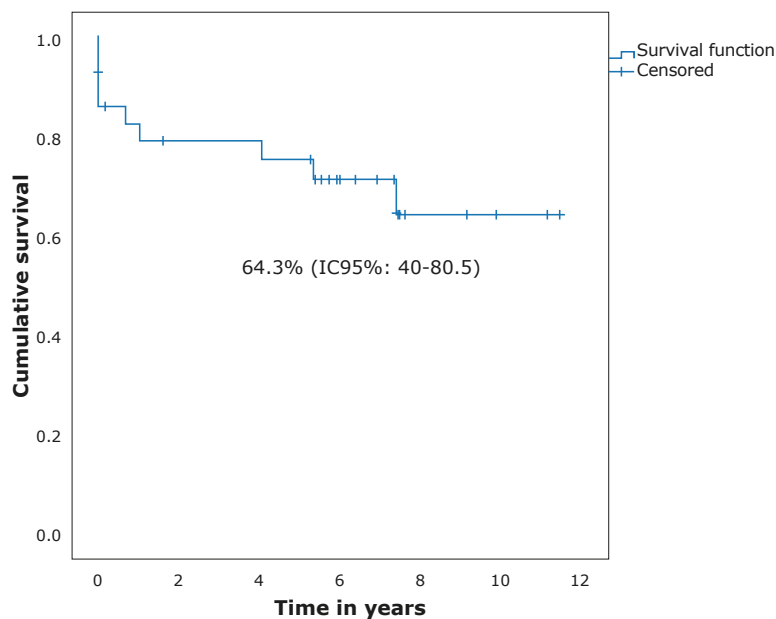


Figure 5. Event-free survival.
Source: Own elaboration.

Discussion

At present, there are few cohort studies on APL conducted exclusively in pediatric populations worldwide,¹⁶⁻¹⁸ especially in Latin America.^{19,20} Moreover, most of the results in this population are derived from research in adult patients. The present study compiles the experience on the treatment of APL at the Fundación Hospital Pediátrico La Misericordia for 7 years, with a follow-up time of up to 11.4 years.

These results provide insight into the response to treatment based on the PETHEMA LPA 99 protocol used for the management of this pediatric cohort. This protocol is based on the administration of ATRA combined with anthracycline chemotherapy, and its implementation achieved OS and EFS rates similar to those achieved in developed countries.^{6,9,11,18,21}

Likewise, a predominance of the male sex in a ratio of 1.5:1 was found, which coincides with the findings reported in other articles.^{16,17,19} The proportion of patients classified as high risk (43%) was higher than that of the GIMEMA group (22.6%) but similar to that reported in Latin America (39.6%).⁹ EFS in the low-risk group was markedly affected because 1 of the patients relapsed and required management with the PETHEMA LPA 99 relapse protocol and, although his condition improved with an autologous transplant, he had a second relapse and died 3 months later, lowering the group's survival rate to 80%. In the medium-risk group, which had 12 patients, survival was 91.7%. These results are similar to those reported by Serephanoglu *et al.*⁹

Although early death is common in patients with APL, it occurred in only 10% of cases in this cohort; none of these patients reached the initiation of chemotherapy, which is consistent with most reports.^{9,16,18,19,22} The main cause of death was intracranial hemorrhage and the moment of greatest risk was the first 15 days after diagnosis, despite intensive transfusion support. Therefore, according to the PETHEMA LPA 99 protocol, it is essential to provide timely and adequate transfusion support

to maintain safe hemostatic levels during the first two weeks after diagnosis; this is possible if the transfusion strategy of platelets, fibrinogen and other coagulation factors is implemented, and if support for the management of leukostasis is provided, aspects which were followed in the cohort analyzed here.^{6,9-13,16,19}

The M3v variant of APL usually has a worse outcome; however, the sample analyzed in the present study was too small for statistical analysis.^{23,24}

Finally, immunophenotyping by flow cytometry in the studied population was positive for the MPO, CD 13, CD 33, CD 117 and CD 64 markers, similar to the findings described by Orfao *et al.*²⁵

One of the limitations of the present study was its retrospective nature and the fact that it was not possible to perform a molecular analysis on all patients. In addition, a limited number of participants were analyzed. However, it should be noted that these patients were exclusively children under 18 years of age at diagnosis and were treated at only one health institution and that APL should be considered a rare subtype of leukemia.

Lastly, and to consider in further studies, it is necessary to perform an individual analysis of the immunophenotype marker CD 56 since some publications mention it as a poor prognostic factor.^{26,27}

Conclusion

Although OS values were lower than those described in pediatric populations in other countries, the implementation of the PETHEMA LPA 99 protocol in the treatment of APL in the study population, in general, showed satisfactory results. Therefore, its use in the pediatric population is suggested, taking into account the adjustments recommended by the protocol regarding the characteristics of this age group.

Conflicts of interest

None stated by the authors.

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