Salud Integral y Comunitaria. 2023; 1:4
doi: 10.62486/sic20234

ORIGINAL

Clinical and epidemiological characterization of chronic lymphoid leukemia patients

Caracterización clínica y epidemiológica de los enfermos de leucemia linfoide crónica

Yanet Montano Medina[1], Yaremys de la Caridad Reinoso Izquierdo[2], Osniel González Hernández[1], Grettel Borrego Cordero[2], Jorge Luis Hernández González[2], Cesar Valdés Sojo[2]

[1]Hospital General Docente "Abel Santamaría Cuadrado". Cuba.
[2]Hospital Pediátrico Provincial Docente "Pepe Portilla". Cuba.

Cite as: Montano Medina Y, Reinoso Izquierdo Y de la C, González Hernández O, Borrego Cordero G, Hernández González JL, Valdés Sojo C. Clinical and epidemiological characterization of chronic lymphoid leukemia patients. Salud Integral y Comunitaria. 2023;1:04. https://doi.org/10.62486/sic20234

Submitted: 06-01-2023 **Revised:** 15-04-2023 **Accepted:** 01-07-2023 **Published:** 02-07-2023

Editor: Prof. Dr. Javier Gonzalez-Argote

ABSTRACT

Introduction: chronic lymphocytic leukemia is the most common malignant hemopathy in the elderly, and in Cuba it represents 9 % of all oncohematologic diseases. Its incidence has increased since the second half of the 20th century. The clinical-epidemiologic characteristics of these patients in Pinar del Río are unknown.
Objective: to clinically and epidemiologically characterize chronic lymphocytic leukemia patients treated at the General Teaching Hospital "Abel Santamaría Cuadrado", 1987-2020.
Materials and Methods: a descriptive, longitudinal and retrospective study was performed. The clinical histories of 120 patients diagnosed with this disease were reviewed and the variables age, sex, clinical manifestations and clinical stage at diagnosis were used.
Results: male patients older than 61 years predominated, general symptoms and stage IV were more frequent at presentation.
Conclusions: the results do not differ from those reported by national reference centers and other international centers dedicated to the care of hematologic malignancies. It is likely that the advanced clinical stage at debut, found in most patients, is related to the delay in diagnosis.

Keywords: Chronic Lymphocytic Leukemia; Chronic Lymphocytic Leukemia; Chronic Lymphoproliferative Syndrome.

RESUMEN

Introducción: la leucemia linfoide crónica es la hemopatía maligna más frecuente en ancianos, y en Cuba constituye el 9 % de todas las enfermedades oncohematológicas. Su incidencia ha aumentado desde la segunda mitad del siglo XX. Se desconocen las características clínico-epidemiológicas de estos enfermos en Pinar del Río.
Objetivo: caracterizar clínica y epidemiológicamente a los enfermos de leucemia linfoide crónica atendidos en el Hospital General Docente "Abel Santamaría Cuadrado", 1987-2020.
Materiales y Método: se realizó un estudio descriptivo, longitudinal y retrospectivo, fueron revisadas las historias clínicas de 120 pacientes diagnosticados con esta enfermedad y se trabajó con las variables edad, sexo, manifestaciones clínicas y estadio clínico al diagnóstico.
Resultados: predominaron los mayores de 61 años del sexo masculino, al debut fueron más frecuentes los síntomas generales y el estadio IV.
Conclusiones: los resultados no se diferencian de los reportados por centros de referencia nacional y otros que internacionalmente se dedican a la atención de hemopatías malignas. Es probable que el estadio clínico

avanzado al debut, encontrado en la mayoría de los pacientes, guarde relación con tardanza en el diagnóstico.

Palabras clave: Leucemia Linfoide Crónica; Leucemia Linfocítica Crónica; Síndrome Linfoproliferativo Crónico.

INTRODUCTION

Chronic lymphoid leukemia (CLL) is an oncohematological entity included within the chronic lymphoproliferative syndrome characterized by the increase of a dysfunctional, clonal lymphoid population of immunophenotype B (> 95 %) and exceptionally T (< 5 %), with a clinical expression that transits from virtually indolent stages, progression, and coexistence with events of autoimmune nature that compromise one or several hemopoietic lines. It is the most frequent leukemia in adults, and its incidence is higher in advanced age.[1]

In 1975, Rai established the first clinical classification of the disease, which is based on the concept that CLL is a disease of progressive accumulation of non-functional lymphocytes.[2] Both this classification and the one proposed by Binet (1981) constitute the European standard for the prognosis of this disease. In the United States, Mexico, and the rest of the American continent, the most widely used is that of Rai et al.[1] The clinical staging or classification systems of Rai and Binet are well-known, simple to apply, and widely used to evaluate tumor volume and predict survival. Patients are classified into three subgroups according to the number of lymphadenopathies, the existence of hepatomegaly, splenomegaly, or both, and anemia, thrombocytopenia, or both.[1,2,4,5]

It has peculiar epidemiological features that distinguish it from other leukemias in many respects. It is one of the most common types of leukemia in the Western Hemisphere and is extremely rare in Asian countries.[6,7]

The incidence varies significantly according to ethnicity, with the highest number of cases reported in Australia, the USA, Ireland, and Italy.[6] The disease is most common in whites, and its frequency decreases in descending order among blacks, Hispanics, American Indians, Ala, ska Natives, Asians, and Pacific Islanders.[8]

Experts estimate a progressive increase in the number of CLL cases each year, but prognoses regarding the number of deaths indicate a steady decline.[8,9,10,11] It is a health problem that is progressively increasing in incidence, but with a tendency to improve survival, thanks to novel treatment regimens.[12]

In Denmark, it constitutes 35-40 % of all leukemias; in Japan, China, and other Asian countries, 3-5 %. In Latin America, the incidence does not reach the rates of Western Europe and Asia, perhaps due to the intense miscegenation of this region. Only four reports were found in the literature that report the estimated incidence of this condition in Latin America, three of them are from Mexico. However, there is a citation in the work of Dr. Redaelli stating that in Brazil, there is an incidence of around 10 %.[6,10] In Cuba, it represents 9 % of all hematological diseases and 12,6 % of leukemias.[13]

The median age at diagnosis was 71 years from 2008 to 2012, according to the SEER database. It is a very uncommon diagnosis before 45 years of age, and before 65 years of age, only 30 % of the total number of patients diagnosed are reported. Considered a disease of old age in Cuba, it presents rates of less than 1 per 100,000 inhabitants up to the age of 55 years.[13]

It is more common in men than in women.[3] National reports denote a high masculinity rate that increases with age; in the group of patients aged 85 years and older, male rates are twice as high as female rates.[13]

It has a typically slow and insidious onset. The most frequent reasons for consultation are enlarged superficial lymph nodes, fatigue, weakness, and weight loss. However, nowadays, in more than 75 % of cases, the disease is discovered accidentally when performing a routine blood count. The appearance of signs and symptoms of the disease is closely related to the infiltration of the lymphoid tissues and bone marrow and alterations in immunity.[14,15]

The suspicion of CLL is established in an older patient who presents with lymphocytosis and adenomegaly or splenomegaly.[10,16] The most relevant clinical characteristic is the presence of adenopathies, which are usually present in 80 %, which, except in very early stages, are present in multiple lymph node territories (cervical, axillary, inguinal) of symmetrical shape, elastic consistency, nonadherent and painless, of variable size which increases in advanced stages.[3,15,17] The hard and painless splenomegaly, which is not usually present in the initial stages of the disease, in isolated cases exceeds the umbilical line and produces abdominal compressive symptoms (sensation of fullness or early satiety). Less frequent is hepatomegaly, of small volume, due to portal lymphoid infiltration.[15]

The most frequent complications of CLL are autoimmune complications, which frequently occur in patients with advanced disease or during treatment with purine analogs. Infections are a significant cause of morbidity and mortality and can be exacerbated by the presence of hypogammaglobulinemia.[18]

The estimated 5-year survival is 81,7 %. Women diagnosed with CLL have overall survival (OS) rates at 5 and 10 years that exceed those of men.[3]

There is a progressive tendency in the world today towards population aging, so diseases formerly of low incidence are gaining prominence and becoming more and more frequent, which requires more significant professional preparation in these issues to ensure the quality of life of our older adults.

Statistical studies predict that by 2030, the Cuban population aged 60 years or more will increase to 30 %, making Cuba one of the most aged countries in Latin America and the world.[19]

Taking into consideration the relatively high frequency of the disease from the fifth decade of life and analyzing that the evolution and survival depend on rapid diagnosis and effective treatment, it was decided to carry out this research with the objective of characterizing the clinical, epidemiological behavior of patients with chronic lymphoid leukemia in Pinar del Río, through the description of the variables: age, sex, clinical manifestations at debut and clinical stage at diagnosis.

METHOD

A descriptive, retrospective, and longitudinal study was carried out at the General Teaching Hospital "Abel Santamaría Cuadrado" covering the period between 1987 and 2020. The universe and the sample coincided and consisted of 120 patients diagnosed with the disease during the study period.

Inclusion criteria: All patients diagnosed with chronic lymphoid leukemia whose medical records reflected the variables selected for the research:

Table 1. Variable's operationalization

Variables	Variable type	Operationalization	
		Scale	Indicator
Age	Continuous quantitative that is grouped in the following intervals	• 40-60 years old • 61-80 years old • 81 and over	Absolute and relative frequencies
Sex	Qualitative Nominal Dichotomous	According to biological sex. • Female • Male	Absolute and relative frequencies
Clinical manifestations at debut	Qualitative nominal polytomous	• Asymptomatic • General symptoms • Infectious processes • Adenopathies • Anemia • Hemorrhages	Absolute and relative frequencies
Clinical stage at diagnosis	Qualitative nominal polytomous	According to the Rai Classification Low Risk: • 0 Intermediate Risk • I • II High Risk • III	Absolute and relative frequencies

Techniques used to obtain the information:

Medical records were reviewed, and data were collected on age, sex, clinical manifestations, and clinical stage at debut.

Methods used:

Theoretical methods made it possible to reach conclusions as well as to interpret, systematize, and deepen the results. Among them are:

- Historical-logical for the study of the theoretical references related to the clinical and epidemiological characteristics of CLL at international and national levels.
- Systemic-structural to determine the relationship between the clinical stage at diagnosis and overall survival in years of patients.
- The modeling allowed defining the indicators for the correct staging of CLL.

As procedures to develop the research process, the following were used:

- Analysis and synthesis to know the qualities of the object of study and its internal relationships during the research.
- Induction and deduction to reach generalizations about the object of study and to identify and understand particular phenomena within it.

- The empirical methods that were used to obtain data on the object of study that allowed solving the scientific problem:
- Document analysis: Review of microhistories of CLL patients of the General Teaching Hospital "Abel Santamaría Cuadrado."
- In addition, searches were carried out in publications: guidelines and regulations in physical or electronic support referred to the topics of study.

Descriptive statistics were used to analyze the information collected in the database according to the variables used.

Methods of data processing and analysis

Analysis and collection of information: The available information was evaluated and purified, selecting that which responded to the objectives set for use in the research.

The elements of descriptive statistics were used to show the quantitative variables (absolute frequencies, %, and average).

A database was created to collect the available information related to the information obtained in the medical records. We used SPSS 10.0 professional software for Windows XP.

Ethical aspects:

This research was carried out under the conditions of respect for the fundamental rights of individuals and the ethical postulates that affect biomedical research with human beings. It is governed by the state regulations of the Ministry of Public Health, in force in the Republic of Cuba. The results obtained from this research will only be used for their presentation in scientific events or for their publication in biomedical journals of recognized prestige.

RESULTS AND DISCUSSION

Table 2 shows the distribution of patients according to age group. The most represented group was 61 to 80 years of age, with 72 patients (60 %), followed by those over 80 years of age. The average age was 71,4 years, with a minimum age of 46 years and a maximum of 94 years. A study conducted by Dr. Porfirio Hernandez (1981) revealed that the average age was 62 years, with a range varying from 49 to 88 years.[20]

In studies conducted in several provinces of Cuba, the age of patients at diagnosis was 65 years or older.[21,22,23]

Table 2. Distribution of patients by age group

Age group	Number	%
40-60	20	16,66
61-80	72	60
> 80	28	23,33
Total	120	100

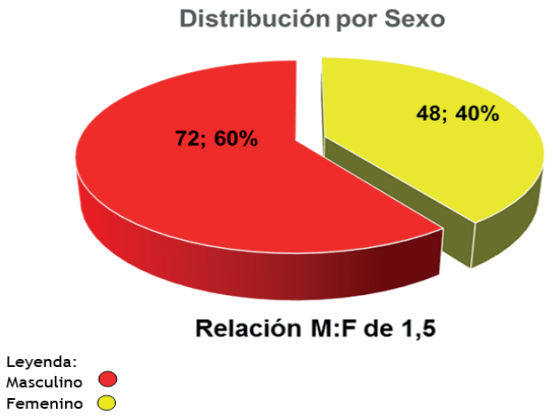

Figure 1. Distribution of patients according to sex.

Other studies from Latin America report an average age of 69,6 and 70 years. [24,25]

The Spanish group of chronic lymphocytic leukemia (GELLC) states that it is the most frequent leukemia in adulthood in their environment. [26] There is a tendency to increase the age at debut, associated to the increase in life expectancy.

The male sex outnumbered the female sex; for every 1,5 men, only 1 woman became ill (Figure 1). CLL is more frequent in men, with a male-female ratio of 1,5-2,0:1,1 The data obtained in studies carried out in Cienfuegos, Santiago de Cuba and Matanzas are similar to those of this research. [21,23,27]

Authors from different latitudes (India, Brazil, United States) also coincide. [3,6,8,28] However, in a study carried out in Togo, out of 87 patients studied, 55 were women, [7] which could be related to the macho culture that favors low attendance to health institutions by men in this African country.

Table 2. Clinical manifestations at debut

Clinical manifestations	Number	%
General symptoms	42	35
Anemia	31	25,8
Adenopathy	27	22,5
Infections	18	15
Hemorrhages	5	4,1
Asymptomatic	16	13,3

Most patients presented with general symptoms at diagnosis (35 %) (Table 2). Only 13,3 % were asymptomatic. Studies carried out in India and Costa Rica show a predominance of asymptomatic patients at debut. [28,29] The international literature states that in many cases, the diagnosis is made by laboratory findings (absolute lymphocytosis) in routine examinations. [1,3] This makes us think about the probability of biases related to the quality of the routine hemogram, which is performed manually by optical microscopy in most laboratories. A correct physical examination and the exclusion of other diseases with adenopathies would help us to complement the diagnosis.

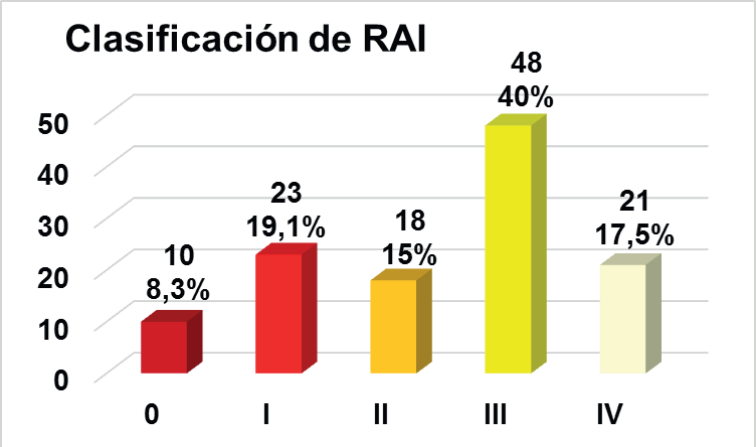

Figure 2. Clinical stage at diagnosis according to Rai classification.

As can be seen in Figure 2, group III, according to the Rai classification, predominated (40 %), and only 8,3 % of the patients were in group 0. This means that most patients were diagnosed in advanced stages of the disease, which has a negative influence on the therapeutic possibilities and survival.

Tejaswi from India reflects a uniform distribution of patients in stages I, II, III, and IV, with 20 %, 25,4 %, 20,8 %, and 21,8 %, respectively. [28]

Rodriguez Brunet observed that 52,1 % of the patients were in advanced stages of the disease. [21] In the Hospital de San Juan de Dios, Costa Rica, 60 % of the patients were classified as stages III and IV. Only 2 % as stage 0. [25] However, there is another study carried out in the same hospital, almost 30 years later, where there were 26 % in stage 0 and 2,6 % in stage III, demonstrating a significant advance in early diagnosis. [29]

Achieving diagnosis in the early stages has an essential impact on patient survival.

The research carried out allowed us to characterize CLL patients according to fundamental clinical and epidemiological aspects, which makes it possible to increase knowledge about this entity and to improve

diagnostic procedures in order to achieve a positive impact on the survival and quality of life of patients with projection towards primary health care.

CONCLUSIONS

The clinical-epidemiological behavior of chronic lymphoid leukemia patients in Pinar del Río is similar to that reported in national and international studies. The age, sex, clinical manifestations, and clinical stage at diagnosis of the disease coincide with data reported by authors from other provinces of Cuba.

The advanced clinical stage at debut, found in most of the patients, is likely related to the delay in diagnosis. There is a probability that clinical and laboratory manifestations typical of CLL are not taken into account, causing late diagnoses that overshadow the prognosis of the patient.

REFERENCES

1. Gibson S, Johnston J, Seftel M. Chronic Lymphocytic Leukemia. En: Wintrobe's Clinical Hematology. 14a. ed. New York: Lippincott Williams Wilkins; 2018. p.4304-95. Available from: https://books.google.com.cu/books?

2. Rai KR. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-234. Disponible en: https://pubmed.ncbi.nlm.nih.gov/1139039/?dopt=Abstract

3. Beutler E, Barry S, Kipps T J, et al. Leucemia linfocítica crónica. In: William´s Hematology. 10th ed. New York: McGraw-Hill. 2021. Disponible en: http://booksmedicos.org

4. Albarrán B, Caballero M, Cabezudo M. Leucemia linfática crónica y linfoma de célula pequeña. Guía de Linfoma. 2020. p 131-141.Complejo Asistencial Universitario de Palencia.

5. Medina A. Guía nacional de leucemia linfática crónica y linfoma linfocítico.2020.4ta Ed. Disponible en: https://www.google.com/url?sa=t&source=web&rct=j&url=https://www.sehh.es/images/stories/recursos/2020/05/18/Guia-Clinica-LLC-abril-2020.pdf&ved=2ahUKEwjqnNaTjbTzAhW1QzABHQ1QCQkQFnoECAQQAQ&usg=AOvVaw0jGFEuWcbWn-PmPoXg6Id_

6. Yamamoto M. Epidemiologia de la leucemia linfocítica crónica. Rev. bras. hematol. hemoter. 2005;27(4):229-232 Disponible en: https://www.scielo.br/j/rbhh/a/JRZtRRqZbwQLC6ymGSGjPtd/?lang=pt

7. Padaro E, Layibo Y, Kueviakoe I. Características de la leucemia linfocítica crónica en Togo. The Pan African Medical Journal. 2019;34:84. Disponible en: https://europepmc.org/article/MED/31934227

8. Farrukh T, Byrd A. Chronic lymphocytic leucemia. Hematology. In: Basic Principles and Practice.7ma ed. Philadelphia: Elsevier. 2018. Disponible en: https://axon.es/ficha/libro/9780323357623/hematology-basic-principles-and-practice-online-and-print.

9. Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. N Engl J Med. 2005; 352: 804-15. Disponible en: https://www.nejm.org/doi/full/10.1056/nejmra041720

10. Cano R, Alvarado M, Álvarez E, Baltazar S. Primer consenso en leucemia linfocítica crónica de la Agrupación Mexicana para el Estudio de la Hematología: epidemiología, diagnóstico y tratamiento. Medicina Universitaria. 2019; 10(40):159-67. Disponible en: https://www.medigraphic.com/cgibin/new/resumen.cgi?IDARTICULO=29171.

11. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2019. Disponible en: https://www.cancer.org/es/cancer/leucemia-linfocitica-cronica/acerca/estadisticas-clave.html

12. Rhodes JM, Barrientos JC. Chemotherapy-free frontline therapy for CLL. A Map for the Changing Landscape of CLL. Hematology. 2020.Disponible en: https://ashpublications.org/hematology/article/2020/1/24/474279/Chemotherapy-free-frontline-therapy-for-CLL-is-it

13. Martin A, Soriano J L. Incidencia de las Leucemias y los Mielomas en Cuba. Rev Cubana Oncol. 2019 ; 14(1):63-70. Disponible en: https://www.bvs.sld.cu/revistas/onc/indice.html

14. Hallek M, Eichhorts B ,Catovsky D. Chronic Lymphocytic Leukemia. Lancet.2018;391(10129):1524-15372019.

Disponible en: https://www.amazon.com

15. Delgado JA, Hernández R. Síndromes linfoproliferativos con expresión leucémica. Leucemia linfocítica crónica. Libro de Hematología (Pregrado).2017. (16) p. 335. Disponible en: https://www.hematoncología.com

16. Swerdlow SH, Campo E, Lee-Harris N, Jaffe ES, Pileri SA, Thiele J, Vardiman J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.2008. 4a Edic. Lyon Disponible en: https://www.iarc.who.int/news-events/who-classification-of-tumours-of-haematopoietic-and-lymphoid-tissues-2/

17. Arias J, Valero J. Leucemia linfocítica crónica. Lux médica. 2013;(25):29-38. Disponible en: https://www.google.com/url?sa=t&source=web&rct=j&url=https://revistas.uaa.mx/index.php/luxmedica/article/view/868/&ved=2ahUKEwjBr-Hnpa_zAhWISDABHZP9C4sQFnoECBIQAQ&usg=AOvVaw3m5ve2CEMVqjJ9GtiaYu7R

18. Rodgers G, Young N. The Bethesda Handbook of Clinical Hematology. 4.ªed, Wolters Kluwer. 2018 (14) p 277-293. Disponible en: http://www.amazon.com

19. ONEI/CEPDE. Proyecciones de la población cubana 2015-2050. Cuba y provincias. La Habana: Oficina Nacional de Estadística e Información; 2020. Disponible en: http://www.onei.gob.cu/node/14710

20. Hernández P. Leucemia linfoide crónica: Aspectos clínicos y biológicos. Rev cub hematol, inmunol y hemoter. 1999; 15 (1): 7-20. Disponible en: https://scholar.google.es/scholar?hl=es&as_sdt=0%2C5&q=leucemia+linfoide+cr%C3%B3nica+&oq=#d=gs_qabs&u=%23p%3DStiFXQgxBT4J

21. Rodríguez M. Aspectos clínico- epidemiológicos de la leucemia linfoide crónica. MEDISAN. 2011; 15 (3): 330-338. Disponible en: http://www.redalyc.org/articulo.oa?id=368445228009

22. Ramírez GK, Bueno RC, Roque PL. Caracterización de pacientes con leucemia linfoide crónica en el hospital ¨Arnaldo Milián Castro¨. Rev. Ciencias Médicas de Pinar del Río. 2019; 15 (3):349-358. Disponible en: htpps://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=92174

23. Caro P R, Orozco P. Evaluación del pronóstico y expectativa de vida de los pacientes afectos de leucemia linfoide crónica en la provincia de Matanzas. Rev Cub Med. 1985;24 1 Disponible en: https://www.google.com/url?sa=t&source=web&rct=j&url=http://www.revmedicina.sld.cu/index.php/med/article/download/2115/1719&ved=2ahUKEwiF_ca5jrTzAhWTSjABHTs6BrUQFnoECAkQAQ&usg=AOvVaw3QNi2fTnmerTkPMMAg4knx

24. Cruz C. Formación de roseta espontánea con eritrocito de ratón en la leucemia linfoide crónica. Rev.cub. hematol. inmunol. hemoter.1987; 3(1): 87-93. Disponible en: htpps://pesquisa.bvsalud.org/portal/resource/pt/lil-53288?src=similardocs

25. Elizondo J. Leucemia linfocítica crónica experiencia acumulada en el servicio de hematología del hospital San Juan de Dios, Costa Rica. Rev. Cost. Cienc. Méd. 1987; 8 (4): :281-284]. Disponible en: https://www.kjim.org/m/journal/view.php?doi=10.3904/kjim.2019.210

26. García JA, Delgado J, Hernández JA, Ramírez A; Loscertales Javier, Jarque I, et all. Actualización de las guías nacionales de consenso del Grupo Español de Leucemia Linfocítica Crónica para el tratamiento y seguimiento de la leucemia linfocítica crónica. Med Clin (Barc). 2017; 148(8):381.1–381.9 Disponible en: www.elsevier.es/medicinaclinica

27. Cabrera M. Sobrevida en leucemias en pacientes mayores de 60 años en Cienfuegos. Colombia Med. 1999; 30(3): 123-26. Disponible en: https://www.google.com/url?sa=t&source=web&rct=j&url=https://www.redalyc.org/pdf/283/28330303.pdf&ved=2ahUKEwjMjKDEjbTzAhV9QjABHSUTBToQFnoECBUQAQ&usg=AOvVaw3ARGl8yDKAxePqswsb3ntc

28. Tejaswi V. Chronic Lymphocytic Leukemia: Real-World Data From India. JCO Glob Oncol. 2020;6:866-872. Disponible en: https://pubmed.ncbi.nlm.nih.gov/27882024/

29. Rojas J. Caracterización clínica y epidemiológica de los pacientes con Leucemia Linfocítica Crónica diagnosticados mediante citometría de flujo en el Hospital San Juan de Dios de marzo 2010 a diciembre

2014. Universidad de Costa Rica. 2016 Disponible en: http://repositorio.sibdi.ucr.ac.cr:8080/jspui/handle/123456789/8912

CONFLICT OF INTEREST

No conflicts of interest exist.

FINANCING

None.

AUTHORSHIP CONTRIBUTION

Conceptualization: Yanet Montano Medina, Yaremys de la Caridad Reinoso Izquierdo, Osniel Gonzalez Hernandez Hernandez, Grettel Borrego Cordero, Jorge Luis Hernandez Gonzalez, Cesar Valdes Sojo.

Research: Yanet Montano Medina, Yaremys de la Caridad Reinoso Izquierdo, Osniel González Hernández, Grettel Borrego Cordero, Jorge Luis Hernández González, Cesar Valdés Sojo.

Writing - initial draft: Yanet Montano Medina, Yaremys de la Caridad Reinoso Izquierdo, Osniel González Hernández, Grettel Borrego Cordero, Jorge Luis Hernández González, Cesar Valdés Sojo.

Writing - proofreading and editing: Yanet Montano Medina, Yaremys de la Caridad Reinoso Izquierdo, Osniel González Hernández, Grettel Borrego Cordero, Jorge Luis Hernández González, Cesar Valdés Sojo.