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Review Article

Challenges in addressing Chronic Lymphocytic Leukemia: when to treat or not to treat?

Desafios na abordagem da Leucemia Linfoide Crônica: quando tratar ou não tratar?

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is a malignant neoplasm characterized by the clonal proliferation of morphologically mature but immunocompetent lymphocytes, which accumulate in the bone marrow, peripheral blood, spleen, and lymph nodes, where the clonal expansion of CD5+ and CD23+ B cells predominantly occurs. The most common chromosomal mutation is del(13q), with *TP53* mutations associated with a worse prognosis. CLL affects middle-aged and elderly patients, being frequently found in Western countries, and male patients are more affected than females. Most individuals are incidentally diagnosed during routine blood tests, as the disease exhibits great heterogeneity in clinical manifestations. The criteria for initiating treatment are based on the Rai and Binet staging systems and the presence of disease-related symptoms. This study aims to present a comprehensive analysis of chronic lymphocytic leukemia and the challenge of when to initiate treatment. To achieve this, a literature review was conducted, searching for scientific articles and electronic media published between 2015 and 2022.

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RESUMO

A leucemia linfoide crônica (LLC) é uma neoplasia maligna caracterizada pela proliferação clonal de linfócitos morfologicamente maduros, mas imuno-incompetentes, que se acumulam em medula óssea, sangue periférico, baço e linfonodos, onde ocorrepredominantemente a expansão clonal de células B CD5+ e CD23+. A mutação cromossômica mais comum é del (13q), estando as mutações de TP53 associadas a um pior prognóstico. A LLC acomete pacientes de meia-idade e idosos, sendo frequentemente encontrada nos países ocidentais, eos pacientes do sexo masculino são mais acometidos do que os de sexo feminino. A maioria dos indivíduos são diagnosticados incidentalmente durante um hemograma de rotina, uma vez que a doença apresenta grande heterogeneidade nas manifestações clínicas. Os critérios para iniciar o tratamento baseiam-se nos sistemas de estadiamento Rai e Binet e na presença de sintomas relacionados à doença.Este estudo objetiva apresentar uma análise abrangente sobre a leucemia linfoide crônica e o desafio de quando iniciar ou não o tratamento. Para tal, foi realizada uma revisão bibliográfica com busca por artigos científicos e meios eletrônicos publicados entre 2015 e 2022.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) or chronic lymphocytic leukemia (CLL) is a malignant neoplasm that falls into the category of chronic lymphoproliferative syndromes characterized as a clonal proliferation of mature and incompetent lymphocytes (CD5+ CD23+)[1, 2]. These lymphocytes proliferate and accumulate in the bone marrow, peripheral blood, spleen, and lymph nodes[2, 3]. CLL can be classified into two groups based on the type of cellular involvement: the B phenotype, which is found in 95% of cases, and the T phenotype, which is found in a smaller proportion of cases[4]. The accumulation of B lymphocytes is not secondary to increased production as commonly occurs in neoplasms but rather due to the long half-life of these cells[2].

A relevant risk factor for developing CLL is family history, as approximately 10% of patients diagnosed with CLL have a present family history[5]. A large portion of individuals has at least one of the four common chromosomal abnormalities: deletion in chromosome 13q14.3 (del[13q]), del(11q), del(17p), or trisomy of chromosome[12]. The most common chromosomal mutation is del(13q). The isolated alteration of (13q14) is associated with a benign course of the disease, while *TP53* mutations are associated with a worse prognosis[6].

CLL is the most common type of leukemia in Western countries, with an average age at diagnosis of 70 years, making it prevalent in the elderly[6-8]. Moreover, male patients are more affected than females, and the Caucasian population also shows a higher prevalence of the disease[2, 3]. Most diagnoses occur incidentally during routine blood tests[2]. The most common clinical manifestations include small, symmetrical lymphadenopathies, primarily in the cervical, supraclavicular, and axillary regions[2, 9]. The criteria for starting treatment are based on Rai and Binet staging and the presentation of symptoms[10]. Asymptomatic patients with stable disease should only be monitored by a specialist[1]. The disease can follow a stable course, become aggressive with frequent recurrences, or transform into aggressive lymphoma, such as diffuse large B-cell lymphoma[11].

To present a comprehensive analysis of chronic lymphocytic leukemia, including the process of hematopoiesis, epidemiology, staging, clinical presentation, diagnosis, and treatment.

MATERIAL AND METHODS

This study is a literature review on chronic lymphocytic leukemia conducted between June and December 2022, through research on virtual platforms such as Pubmed, Scientific Electronic Library Online (SCIELO), and Latin American and Caribbean Literature in Health Sciences (LILACS). The search descriptors used were "chronic lymphocytic leukemia," "leukemia," "hematopoiesis," and "treatment," combined through the boolean operator "and." Based on the reading of the abstracts of the found articles, articles in Portuguese, English, and Spanish published on the aforementioned platforms between 2015 and 2022 that addressed chronic lymphocytic leukemia were accepted.

This manuscript was translated with the assistance of ChatGPT, an AI language model developed by OpenAI.

RESULTS AND DISCUSSION

HEMATOPOIESIS

The bone marrow is the most relevant hematopoietic site during childhood and adulthood[12]. Cells develop in the bone marrow and, when mature, are relocated to the sinusoidal spaces in the marrow microcirculation and subsequently to the peripheral blood circulation. Hematopoiesis is a process of formation, development, and maturation of blood cells through the pluripotent stem cell, which can self-renew and give rise to different cell lineages. Precursor cells

respond to growth factors, increasing the selective production of specific blood cell lineages according to need[13].

For proper hematopoiesis occur, a microenvironment with hematopoietic cells without molecular alterations, stromal cells including fibroblasts, adipocytes, extracellular matrix, and endothelial cells is necessary[12]. Pluripotent stem cells give rise to the initial hematopoietic progenitors: the common myeloid cell from which the granulocytic, monocytic, erythroid, and platelet lineages are produced; and the common lymphoid cell from which the B, T, and natural killer cell lineages are produced[14].

Lymphopoiesis is highlighted for understanding the development of CLL. In this process, precursor cells are lymphoblasts that differentiate and mature into prolymphocytes and lymphocytes[12, 14]. Erythrocytes, granulocytes, monocytes, and platelets are synthesized only in the bone marrow, while lymphocytes are synthesized in the bone marrow, lymph nodes, spleen, and thymus[12].

LEUKEMIAS

Leukemia refers to the clonal proliferation of leukemic cells in the bone marrow, resulting in elevated cells of a specific leukocyte lineage affecting peripheral blood. Leukemias can be classified according to lineage and progenitor cell (lymphoid or myeloid) and maturation phase (acute or chronic)[14]. The main types of leukemias are Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML), Acute Lymphoid Leukemia (ALL), and Chronic Lymphoid Leukemia (CLL)[12].

Leukemias comprise a group of hematological neoplasms of myeloid or lymphoid lineage, in which cells undergo a mutation process expressing oncogenes and loss of function of tumor suppressor genes, resulting in the clonal expansion of leukemic cells[14].

EPIDEMIOLOGY

In chronic lymphocytic leukemia, there is an exponentially high frequency according to age group, with an average presentation at 70 years of age and a higher number of cases in the 65-74 age range[5, 15]. However, this data is not restricted as the incidence varies according to race/ethnicity: white > black > Hispanic > Asian[5]. There is a strong predominance in males compared to females. CLL is more common in Western countries, representing almost 25% of all leukemias[15]. Its incidence is lower among Asians and higher in Jews[6, 15].

In Brazil, males are more affected by lymphoid leukemia (LL) than females. Furthermore, a predominance was observed in the Southeast, Northeast, and South regions, respectively, from 2016 to 2020[16].

STAGING

CLL presents a wide spectrum, ranging from a slow and indolent course to the accelerated progression of the disease[17]. Therefore, individuals with CLL should undergo risk stratification[10]. The most used staging system for chronic lymphocytic leukemia is called Rai and Binet staging, covering clinical parameters such as physical examination and laboratory tests (complete blood count) without using imaging exams[9, 17]. Despite being widely used as a prognostic tool, this staging has some limitations when dealing with individual patients[17].

According to the Rai and Binet staging system, CLL patients are classified into low, intermediate, and high-risk groups. In the Rai staging, the disease is defined as low risk in patients with lymphocytosis with leukemic cells in the blood and/or marrow (lymphoid cells >30%). Individuals with lymphocytosis, lymphadenomegaly in any region, and splenomegaly and/or hepatomegaly (palpable or non-palpable lymph nodes) are classified as having intermediate-risk disease (previously considered Rai stage I or stage II). Patients with anemia (hb below 11g/dl) or thrombocytopenia (platelet count below 100 - 109/L) have high-risk disease (previously stage IV)[6]. The bone marrow smear is shown in **Figure 1**.

Binet staging is based on the number of

sites involved, i.e., the presence of lymph nodes larger than 1 cm in diameter and whether there is anemia or thrombocytopenia. The affected regions are: head and neck, including Waldeyer's ring; axillae (both axillae affected); groins, including superficial femoral; palpable spleen; palpable liver. Binet stage A is classified as Hb ≥ 10 g/dL and platelets ≥100 - 109/L and up to two involved sites; stage B as Hb ≥ 10 g/dL and platelets ≥ 100 - 109/L and organomegaly greater than defined for stage A; and stage C as Hb below 10 g/dL and/or platelet count below 100 - 109/EU[6].

TREATMENT CRITERIA

Treatment is based on the criteria established by the Rai and Binet staging systems and the presence of disease-related symptoms[10].

In clinical practice, newly diagnosed patients predominantly present with asymptomatic and early-stage disease (Rai O; Binet A). Early treatment in these cases does not result in any benefit and may even cause harm. This does not mean that these patients are excluded from clinical follow-up, as they should receive monitoring without therapy until disease progression[9].

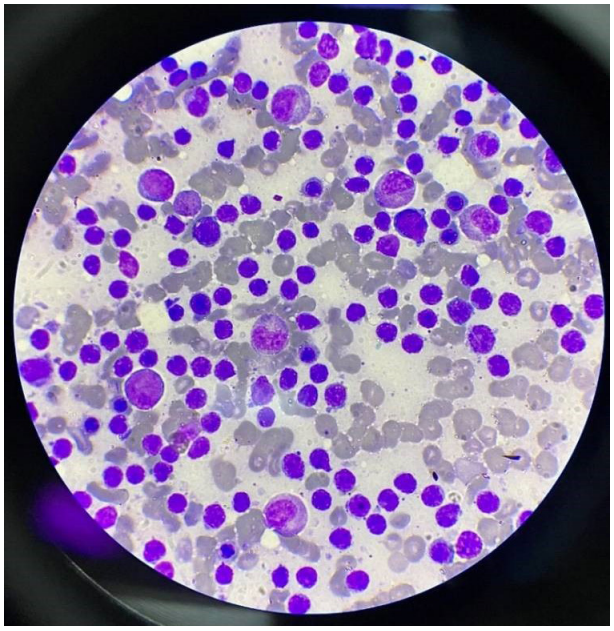

Figure 1 – Bone Marrow Smear: The lymphocytes are small, basophilic, mature with a narrow rim of cytoplasm and a dense nucleus without nucleoli.

Cases with advanced disease (Rai stage III and IV; Binet stage C) and patients with symptoms benefit from initiating treatment. By convention, symptomatic or active disease is defined through: indications of progressive bone marrow insufficiency (anemia [hemoglobin concentration <11g/dL for Rai staging and <10g/dL for Binet staging] or thrombocytopenia [platelet count below 100x109/L]); massive, progressive, or symptomatic splenomegaly or lymphadenopathy; autoimmune hemolytic anemia and/or immune thrombocytopenia unresponsive to corticosteroids[9].

Constitutional symptoms defined as persistent and unexplained fever (temperature > 38° C) and/or weight loss (>10% of baseline weight in less than 6 months) and/or severe night sweats may also represent a considerable indication for treatment[12].

Rapidly progressive lymphocytosis with a lymphocyte doubling time of less than six months may also be an indication for treatment. However, when lymphocyte doubling time is used as the sole criterion for initiating treatment, initial blood lymphocyte counts should be greater than 30,000 cells per microliter, and a careful clinical evaluation should exclude other factors contributing to lymphocytosis or lymphadenopathy, such as infectious conditions[9].

THERAPIES USED

CLL is a highly heterogeneous disease, and no single approach is applicable to all patients. Patient age, ability to tolerate treatment, *TP53* deletion/mutation, and the presence of autoimmune problems generally affect treatment choice[18].

First-line treatment is conditioned to patients under 65 years old with good performance status and in Europe to patients with creatinine clearance of 70 mL/min or more, in addition to a comorbidity index score of 6 or less, being good candidates for chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR). First-line treatment with FCR is associated with a 90% effective response rate. Prolonged myelosuppression, early and late infections, and

secondary cancer remain major concerns with this regimen[12].

Bendamustine associated with rituximab (BR) shows better tolerability, making this regimen suitable for older patients, demonstrating efficacy comparable to FCR. For patients with 17p deletion or *TP53* mutation, current therapy consists of using ibrutinib, an oral selective and irreversible inhibitor of Bruton tyrosine kinase (BTK). In frail patients with comorbidities, first-line treatment can be administered with a combination of chlorambucil and an anti-CD20 monoclonal antibody[7].

Despite therapeutic advancements, the treatment of patients with relapsed or refractory CLL remains a matter requiring attention. A significant challenge is that this population presents numerous adverse factors such as IGHV and *TP53* mutation. The use of ibrutinib as rescue therapy has considerably changed the management and prognosis of relapsed CLL patients[12].

The most common options for patients who relapse after chemoimmunotherapy and/or ibrutinib are idelalisib (in combination with rituximab) and venetoclax. Idelalisib is a potent and selective inhibitor of PI3K-delta, a kinase in the B-cell receptor signaling pathway, which is constitutively activated in CLL cells. Venetoclax is a BH3 mimetic targeting BCL2, a protein overexpressed in CLL[12].

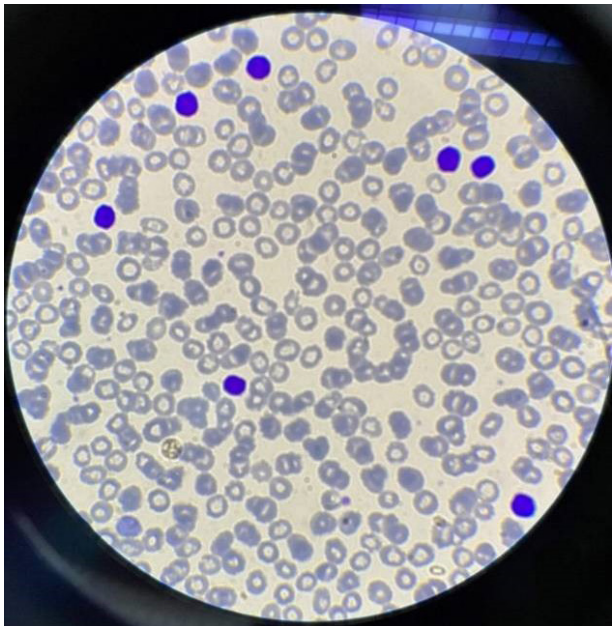

Figure 2 – Peripheral Blood Smear: The lymphocytes are small, basophilic cells with a dense nucleus without a nucleolus.

Chronic lymphocytic leukemia is a heterogeneous neoplastic disease; thus, no standard approach can be applied to all patients. Age, performance status, comorbidities, 17p deletion, or *TP53* mutation affect the treatment choice for certain individuals, often becoming a challenge for the attending hematologist. Treatment criteria are based on Rai and Binet staging and symptom presentation. It is not recommended to initiate treatment in the asymptomatic stage of the disease, which is often not understood by the patient, resulting in discomfort in the doctor-patient relationship.

REFERENCES

1. Jacque N, Leblond V. [Chronic lymphocytic leukemia]. Presse Med. 2019;48(7-8 Pt 1):807-15.
2. Marrero YT, Suárez VM, Ballester AS, Domínguez GD. Leucemia linfoide crónica de células B: revisión de sus aspectos etiopatogénicos, moleculares y pronósticos. Revista Cubana de Hematología, Inmunología y Hemoterapia. 2019;35(1):e927.
3. García KR, Rodríguez CdlCB, Pérez LR, Sacerio AL. Caracterización de pacientes con leucemia linfoide crónica en el Hospital Provincial Universitario "Arnaldo Milián Castro". Universidad Médica Pinareña,. 2019;15(2):349-58.
4. Martín PG, Puerta JMP, Chacón MJ. Leucemia linfática crónica B. Diagnóstico, pronóstico y tratamiento. Actual Med. 2017;100(800):52-3.
5. Cerhan JR, Slager SL. Familial predisposition and genetic risk factors for lymphoma. Blood. 2015;126(20):2265-73.
6. Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol. 2021;96(12):1679-705.
7. Chiorazzi N, Chen SS, Rai KR. Chronic Lymphocytic Leukemia. Cold Spring Harb Perspect Med. 2021;11(2).
8. Kikushige Y. Pathogenesis of chronic lymphocytic leukemia and the development of nov-

el therapeutic strategies. J Clin Exp Hematop. 2020;60(4):146-58.
9. Abreu GM, de Sousa SC, Gomes EV. Leucemia Linfoide e Mieloide: Uma breve revisão narrativa / Lymphoid and Myeloid Leukemia: A brief narrative review. Brazilian Journal of Development. 2021;7(8):80666-81.
10. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. Lancet. 2018;391(10129):1524-37.
11. Delgado J, Nadeu F, Colomer D, Campo E. Chronic lymphocytic leukemia: from molecular pathogenesis to novel therapeutic strategies. Haematologica. 2020;105(9):2205-17.
12. Lira AdO, Pereira A. Métodos laboratoriais utilizados para o diagnóstico da leucemia linfoide crônica: uma revisão / Laboratory methods used in the diagnosis of chronic lymphocytic leukemia: a review. Brazilian Journal of Health Review. 2019;2(4):2862-932.
13. Chapman J, Zhang Y. Histology, Hematopoiesis. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Yaoping Zhang declares no relevant financial relationships with ineligible companies.2024.
14. Bispo JAB, Pinheiro PS, Kobetz EK. Epidemiology and Etiology of Leukemia and Lymphoma. Cold Spring Harb Perspect Med. 2020;10(6).
15. Strati P, Jain N, O'Brien S. Chronic Lymphocytic Leukemia: Diagnosis and Treatment. Mayo Clin Proc. 2018;93(5):651-64.
16. Bassani BFB, Schuster AL, Consoni PRC. Perfil epidemiológico de mortalidade por leucemia linfóide no Brasil nos últimos 4 anoS. Hematology, Transfusion and Cell Therapy. 2021;43:S118.
17. Sharma S, Rai KR. Chronic lymphocytic leukemia (CLL) treatment: So many choices, such great options. Cancer. 2019;125(9):1432-40.
18. Munir T. Chronic lymphocytic leukemia. Hematology. 2015;20(4):245-6.