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CASE REPORT

Prognostic Factors and Management in Chronic Lymphocytic Leukemia in Young Patients: A Case Report

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ABSTRACT

Chronic lymphocytic leukemia is the most common form of leukemia found in the West, primarily affecting individuals between 65 and 72 years old, with a survival rate of approximately 10 years. The aim of this study was to describe the clinical presentation of chronic lymphocytic leukemia by relating it to a case of a young patient wiyh this disease, seeking to discuss possible clinical factors associated with prognosis. To this end, a review of the patient's medical record was conducted, along with a search of the scientific literature, and articles presenting relevant data were selected for this study. Based on the research conducted, the importance of using the Chronic Lymphocytic Leukemia International Prognostic Index, which considers disease progression and aids in therapy, was noted. Additionally, it was observed that chronic lymphocytic leukemia is a disease that can significantly affect the life expectancy of affected individuals, especially older ones. However, despite the patient being young, her prognosis tends to be unfavorable, mainly due to the presence of unmutated immunoglobulin heavy chain variable region gene, which is associated with a poorer response to treatment and lower overall survival.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the western hemisphere[1], affecting mainly individuals between the ages of 65 and 72. However, recent studies indicate that approximately 10-20% are diagnosed before 55 years old[2]. The median survival of patients with CLL is approximately 10 years, but individual prognosis can vary considerably[3]. Young patients tend to have a longer survival time and account for only 3.7% of deaths related to the disease[2,4]. Individuals under 45 years of age are more likely to have intermediate (I and II) and high (III and IV) Rai risk and to have unmutated IGHV when compared to individuals aged 46-50 or 51-55 years[1]. Patients with CLL under 55 years of age have a shorter survival rate compared to the population of the same age and sex, but the survival rate of young patients with CLL is higher than that of patients over 55 years of age with CLL[1].

Chronic lymphocytic leukemia is characterized by the proliferation and accumulation of mature B lymphocytes in the bone marrow, peripheral blood, and secondary lymphoid tissue. The patient may present with asymptomatic lymphocytosis, lymph node enlargement, hypogammaglobulinemia, anemia and thrombocytopenia.

The diagnosis is confirmed by the presence of sustained monoclonal lymphocytosis greater than 5,000-10,000/mm^3 in two tests performed at least one month apart, and by positivity of markers of mature B lymphocytes on flow cytometry (CD5, CD19, CD20, and CD23)[5].

Two staging systems are commonly used and are based on physical examination and blood count results. They are called the Rai and Binet staging systems[6]. They stratify patients with CLL into three risk groups: low (Rai 0, Binet A), intermediate (Rai I/II, Binet B) and high (Rai III/IV, Binet C), showing an estimated median survival of >10 years, 5-7 years and 1-3 years, respectively. However, they cannot predict individual evolutionary variations and only reflect the tumor burden[7].

Currently, 70-80% of patients are diagnosed incidentally in routine blood tests and will have the disease in an early stage (Rai 0 or I)[6], and more than half of these will not present secondary events to the disease[7]. Treatment depends on the patient's clinical condition and stage, and is indicated for patients in Rai stages III and IV and Binet C, that is, those who present symptoms, such as those associated with anemia and thrombocytopenia, for example. Treatment should be individualized, but younger patients tend to respond better to immunochemotherapy[2] when they do not have biological factors of poor prognosis. In addition, hematopoietic stem cell transplantation and participation in clinical trials should be considered for these patients[2]. Generally, the response rate to treatment and survival are better in females[6].

Patients with CLL may present different genetic mutations, the most common being deletions of chromosomes 13q, 11q and 17p. Patients with deletion of chromosome 11q have a better prognosis, while those with deletion of 17p have a worse prognosis[8,9]. Deletion of 17p usually indicates poor response to some conventional treatments and a median survival of less than three years[7].

Mutations in the TP53 gene are markers of poor prognosis and disease resistant to chemotherapy treatment. Therefore, testing for mutations of the gene and deletions of the corresponding locus [del(17p)] is essential for making decisions about treatment[10]. The mutation status of the immunoglobulin heavy chain variable region (IGVH) gene is another important prognostic factor in the disease. Studies show that patients with unmutated IGVH had shorter survival from diagnosis compared to patients with the mutation, in addition to shorter remission duration and survival from the start of chemoimmunotherapy[11].

Case Report

A 31-year-old caucasian female patient was referred from the Emergency Room for a hematology consultation due to lymphocytosis in the blood count. At the time, lymphocytes were 17,712/mm^3; red and

platelet series were normal. A peripheral blood smear showed Around 56% small, mature lymphocytes. Her physical examination was also normal. Flow cytometry of peripheral blood confirmed the diagnosis of CLL with the following immunophenotypic characteristics: 64.5% of CD45+, CD19+, CD20+, CD5+, CD200+, partial CD23 monoclonal lymphocytes, with lambda light chain restriction. The markers CD3, CD10, CD25, CD38, CD56, CD79b were negative.

However, due to the patient's age, it was decided to evaluate the cytogenetic profile and mutational status by Fluorescence in situ hybridization (FISH). This analysis did not reveal any chromosomal abnormalities (46,XX), such as deletion 13q, trisomy 12, deletion 11q, or deletion 17p. However, molecular analysis revealed unmutated IGHV genes.

The patient was asymptomatic since diagnosis, with no evidence of lymphadenopathy, splenomegaly, or anemia. The patient began "watch and wait" follow-up because she was always asymptomatic. She started clinical consultations every four months, having currently been under follow-up for four years, with no changes in the condition, that is, no indication of treatment.

Last blood count shows that lymphocytosis is 42,169/mm³. β2 microglobulin values ranged from 1.388 to 1.733 mg/L and lactic dehydrogenase from 120 to 353 U/L.

Table 1. Patient's blood counts during treatment.

Date	06/06/2019	24/08/2020	02/09/2021	19/09/2022	03/03/2023
HB (g/dL)	14,0	15,3	14,2	14,4	13,4
HCT (%)	43,6	47,0	47,4	48,2	44,8
MCV (fL)	89,2	90,4	96,5	97,6	97,6
Leukocytes (/mm³)	30.400	49.000	54.860	53.160	48.470
Neutrophils (/mm³)	7.890	6.860	13.166	5.848	4.847
Lymphocytes (/mm³)	17.000	40.180	40.596	45.718	42.169
Platelets (/mm³)	297.000	309.000	292.000	260.000	244.000

Discussion

Despite the literature stating the prevalence of CLL in the elderly (> 55 years), the patient in question is young and, presenting only lymphocytosis on the complete blood count, as most of the cases described. But she shows a sign of bad prognosis: the unmutated IGHV gene[12,13]. It is also observed, in younger patients, that it is more common to have a positive family history for CLL, which does not happen to this patient[12]. However, given that the patient is asymptomatic, treatment was not necessary[14].

Chronic lymphocytic leukemia is classified according to the "CLL Prognostic Index" (CLL-IPI), which takes into account 5 characteristics: presence of deletion 17p on FISH or mutation of the TP53 gene; unmutated IGHV; β2 microglobulin > 3,5 mg/L; RAI stage showing high risk and age > 65 years. That scoring system allows the classification into: low, intermediate and high risk[14,15]. The CLL-IPI is based on the Rai/Binet staging systems, which are easy to apply and allow for objective and standardized patient assessment. There is no consensus on which system is better, and preference varies by country and/or oncology-hematology service. In the past, these systems were applied in isolation, but with further research and understanding of the disease, other variants have been considered important for

classification and prognosis, leading to the current CLL-IPI[13]. To calculate this patient's CLL-IPI score, her Rai score needed to be determined. Considering her physical examination was normal (no lymphadenopathy) and her only laboratory abnormality was lymphocytosis, she falls under Rai 0.

Chronic lymphocytic leukemia in young patients poses unique prognostic challenges. Young age itself does not necessarily confer a better prognosis, as disease biology often plays a more significant role. It is known that, in addition to the higher prevalence of CLL in older ages, the incidence of the disease also increases considerably with advancing age[15]. The incidence of CLL steadily rises with age, and several mechanisms link aging with disease development. There is a growing body of evidence highlighting the complex relationship between cellular senescence, the cell cycle and the immune system of the disease[11,16].

The presence of unmutated IGHV in our patient places her at intermediate risk for disease progression, despite her young age and lack of adverse cytogenetic findings. The prognostic value of IGHV mutation status is well-documented, with unmutated IGHV being associated with shorter time to first treatment (TTFT) and inferior overall survival (OS) compared to mutated IGHV[9,10,11]. The mutated IGHV status in CLL is considered a favorable prognostic factor for the disease in terms of response duration, quality, and overall survival. The mechanism by which this occurs is not entirely understood, but one hypothesis is that when the cellular IGHV mutation status is unmutated, it is characterized by rapid cell replication, which may be responsible for a poorer response to traditional drug therapy[16,17].

Discrepancies have been observed in patients with unmutated IGHV regarding overall survival (OS) and progression-free survival (PFS). For instance, a PFS range of 9 to 18 years is seen in patients with mutated IGHV compared to 1 to 5 years for those with unmutated IGHV. Similarly, a range of 17 to 25 years is observed in patients with a mutated gene and 3 to 10 years in those with an unmutated gene when using chemoimmunotherapy (CIT). This does not apply to newer agents targeting B-cell receptor (BCR) pathway kinases, such as Bruton's tyrosine kinase inhibitors. These drugs, which work by binding to the receptor and preventing the proliferation of both malignant and normal B cells, have shown more significant responses in patients with unmutated IGHV. This could be explained by the higher avidity of these cells in BCR signaling, as seen with Ibrutinib[17,18].

In addition to IGHV status, chromosomal abnormalities such as deletion 17p and TP53 mutations are crucial in determining the prognosis and therapeutic options in CLL[12]. Although our patient did not have any high-risk cytogenetic features, her unmutated IGHV status underscores the need for close monitoring. Studies have shown that patients with unmutated IGHV are less likely to respond to traditional chemotherapy regimens, such as fludarabine-based therapy, and may benefit from newer targeted therapies, such as Bruton's tyrosine kinase (BTK) inhibitors or BCL-2 inhibitors[13, 14,15]. The p53 gene is a tumor suppressor gene that encodes a nuclear phosphoprotein crucial for cell cycle control, DNA repair, and apoptosis induction. Under stress conditions, particularly DNA damage, the p53 protein blocks the cell cycle, allowing for DNA repair or promoting apoptosis. The mutated form of p53 is unable to control cell proliferation, leading to inefficient DNA repair and the emergence of genetically unstable cells. In hematologic neoplasms, these mutations, often point mutations, are less frequently observed than in solid tumors[19]. Patients with CLL with del 17p or TP53 gene mutations are considered high risk due to poorer responses to initial treatment or earlier relapse[13]. Since the patient does not have such alterations, she does not meet this poor prognostic criteria.

As for β2-microglobulin, it is a serum tumor marker whose main function as a prognostic factor is the assessment of tumor burden. This marker is favorable for the patient, as her β2-microglobulin ranged between 1.388 and 1.733 mg/L and did not exceed 3.5 mg/L[13].

We identified that the CLL International Prognostic Index (CLL-IPI), which integrates clinical and molecular factors including age, clinical stage, IGHV mutation status, and cytogenetic abnormalities, provides a more comprehensive risk stratification tool[16]. Using the CLL-IPI, our patient would be classified as intermediate-risk, with an estimated 5-year OS of 79%[17]. This highlights the need for individualized treatment plans, particularly in younger patients who may live for decades with the disease[18].

Management of young patients with CLL also involves consideration of long-term toxicities and quality of life. Given the availability of novel agents with better side effect profiles and durable responses, there is a growing preference for targeted therapies over chemoimmunotherapy in younger patients[19,20]. Bruton's tyrosine kinase (BTK) inhibitors, such as Ibrutinib, and BCL-2 inhibitors, such as Venetoclax, have shown efficacy in both frontline and relapsed CLL settings, particularly in patients with high-risk features[21,22]. And that is our plan for her when treatment appears to be required.

Conclusion

This case illustrates the complexity of managing CLL in a young patient. Despite the absence of high-risk cytogenetic abnormalities, the presence of unmutated IGHV confers an intermediate-risk prognosis and emphasizes the need for careful monitoring. With the advent of targeted therapies, the treatment landscape for CLL continues to evolve, offering promising options for patients with high-risk disease features. The long-term management of young patients with CLL should prioritize not only disease control but also the preservation of quality of life, given the potential for many years of survival.

Conflict of Interest:

None

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None

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