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Case Report

Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia: A Case Report

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Abstract

We present the case of a 57-year-old male patient diagnosed with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). The initial diagnosis included clinical findings such as hepatomegaly and splenomegaly, accompanied by extreme leukocytosis. Molecular studies confirmed the presence of the Philadelphia chromosome, with cytogenetic studies showing resistance to tyrosine kinase inhibitors such as dasatinib. The patient received multiple treatments, including imatinib, dasatinib, and later bosutinib. Complete blood counts and bone biopsies showed infiltration of lymphoid blasts and hematologic complications such as neutropenia and severe anemia. During follow-up, no hematologic or molecular response was observed. Management was limited by the patient's refusal to receive intensive chemotherapy and the lack of availability of allogeneic transplantation in Honduras.

Keywords: *Acute Lymphoblastic Leukemia; Philadelphia Chromosome; Blastosis; Tyrosine Kinase Inhibitors; Neutropenia*

Introduction

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the presence of the t(9;22) translocation, which generates the BCR-ABL1 fusion gene. This genetic alteration is associated with an unfavorable prognosis, representing approximately 25% of ALL in adults and between 2% and 3% in children [1].

The introduction of tyrosine kinase inhibitors (TKIs), such as imatinib and dasatinib, has significantly improved overall survival and disease-free survival in patients with Ph+ ALL. These agents, combined with chemotherapy, have been shown to increase complete remission rates and reduce the incidence of relapses [2].

Despite these advances, allogeneic hematopoietic stem cell transplantation remains a fundamental therapeutic option to consolidate remission in patients with Ph+ ALL, especially in those with high-risk factors or suboptimal response to initial treatment. However, the availability of compatible donors and complications associated with transplantation limit its universal application [3].

A standardized risk assessment for each patient is essential to decide on the initiation of chemotherapy and to consider additional interventions. Instruments that estimate life expectancy, treatment tolerance and functionality can be helpful in therapeutic decision-making, especially in patients over 60 years of age [4].

Case Presentation

A 57-year-old married man, Catholic and with complete primary education, resident of Comayagua, Honduras, presents with a history of chronic arterial hypertension controlled with enalapril and a previous appendectomy. He does not report the use of toxic substances. Three months prior to his initial consultation, he experienced weight loss, anorexia, nocturnal diaphoresis, and progressive dyspnea with minimal effort. He went to the internal medicine service on December 30, 2022, where the physical examination showed a deteriorated general condition, with signs of pulmonary condensation in the right hemithorax, 5 cm hepatomegaly, and 10 cm splenomegaly below the costal margin.

Initial studies included a chest x-ray that showed right lower lobe condensation consistent with pneumonia and a complete blood count that revealed extreme leukocytosis (129.9/mm^3, neutrophils 111.8/mm^3, basophils 12.3/mm^3), hemoglobin 12 g/dL, and platelets 231,000/mm^3. Renal and liver function were within normal parameters, and viral serologies were negative. The initial diagnosis by internal medicine was chronic myeloproliferative syndrome, for which the patient was referred to the hematology department.

Specialized studies performed in January 2023 included a peripheral blood smear that showed less than 10% myeloid immature blasts and a bone marrow biopsy that confirmed chronic phase chronic myeloid leukemia. Molecular analysis revealed the presence of the Philadelphia chromosome (47.65% is, MR 0.32). Treatment was started with imatinib 400 mg/day, later increased to 800 mg/day without achieving hematological or molecular response. However, serial blood counts showed disease progression with an increase in the blast count and a decrease in hemoglobin (up to 6.5 g/dl). due to progression, treatment was changed to dasatinib 50 mg every 12 hours. After 45 days with dasatinib, transformation to the acute phase was observed with a percentage of lymphoid blasts in the peripheral blood smear greater than 20%. A new bone marrow biopsy was performed which showed unclassified acute leukemia, with 90% of blasts in the bone marrow. Flow cytometry identified an immunophenotype of acute lymphoblastic leukemia of common phenotype B precursors (cd10, cd19, cd34, cd38, cd58 and cd66).

The patient's management was complicated by febrile neutropenia, severe anemia, and gastrointestinal bleeding. In addition, the patient refused intensive chemotherapy, and the option of allogeneic transplantation was not available in Honduras. It was decided to continue with tyrosine kinase inhibitors.

New molecular studies were performed with a positive Philadelphia chromosome, cytogenetic studies showed genomic alterations in F317L that confer resistance to treatment with dasatinib and nilotinib, so they are suspended and the patient is switched to bosutinib 400 mg/day (without achieving a major hematological and molecular response). Currently, the patient is under continuous evaluation with hematological and molecular studies, continuing with oral therapy and palliative management for hematological complications. The patient is receiving treatment with imatinib, dasatinib, nilotinib, bosutinib, without achieving a hematological response or a major molecular response. The use of ponatinib, which is the gold standard in patients with genomic alterations, is not used due to the difficulty in introducing it into our country.

The patient is offered treatment with systemic chemotherapy which was initially refused but then upon re-staging with biopsy and flow cytometry study the diagnosis was confirmed again as high-risk Philadelphia chromosome positive acute lymphoblastic leukemia. It was decided to start systemic treatment with chemotherapy (GATLA2022 regimen used) with third generation tyrosine kinase inhibitors asciminib (40 mg every 12 hours) achieving minimal negative residual and deep hematological and molecular response post induction chemotherapy performed at the sixth week of treatment, at the end of the regimen with systemic chemotherapy together with tyrosine kinase inhibitors the patient is re-evaluated with a minimal negative residual / deep hematological and molecular response; at 3 and 6 months after the end of systemic treatment, he maintains minimal negative residual with deep hematological and molecular response.

Currently achieving complete hematological and molecular remission. evidencing the response to systemic chemotherapy + third-generation tyrosine kinase inhibitors (asciminib) in high-risk Philadelphia chromosome-positive lymphoblastic leukemias. Achieving an overall survival of +- 3 to 5 years with the use of this therapy, always considering hematopoietic progenitor cell transplantation with definitive treatment. Currently achieving complete hematological and molecular remission.

Discussion

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) represents an aggressive variant of leukemia, characterized by the presence of the t(9;22) translocation, which gives rise to the BCR-ABL1 fusion protein. This genetic abnormality confers to leukemic cells a proliferative advantage and resistance to apoptosis, which has historically been associated with a poor prognosis [5].

The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of Ph+ ALL. Imatinib, the first approved TKI, was shown to significantly improve complete remission rates and overall survival in patients with Ph+ ALL. However, resistance and relapse remain major challenges [5].

Dasatinib, nilotinib, bosutinib, second-generation TKIs, have shown efficacy in patients with resistance or intolerance to imatinib. Its ability to inhibit multiple kinases, including SRC, makes it effective in cases with mutations that confer resistance to imatinib. Studies have reported deep molecular response rates with dasatinib, although its use may be associated with adverse effects such as pleural effusion and cytopenias [6].

Ponatinib, a third-generation TKI, has been designed to overcome mutations such as T315I, which confer resistance to first- and second-generation TKIs. Clinical studies have demonstrated its efficacy in patients with refractory or resistant Ph+ ALL, although its safety profile requires monitoring due to the risk of thromboembolic events [7].

Asciminib (Scemblix), a third-generation TKI, has been designed to overcome mutations such as T315I and other mutational variants that confer resistance to first- and second-generation TKIs. Clinical studies have demonstrated its efficacy in patients with refractory or resistant Ph+ ALL, although its safety profile requires monitoring for respiratory infections, cytopenias, and transaminases.

The combination of TKIs with chemotherapy has improved outcomes in Ph+ ALL. However, chemotherapy-free regimens, combining TKIs with agents such as blinatumomab, a bispecific antibody, have shown promising results in inducing deep remissions with lower toxicity. These approaches could be especially beneficial in older patients or those with comorbidities [8].

Allogeneic hematopoietic stem cell transplantation has been considered the standard for consolidating remission in Ph+ ALL. However, with the availability of more potent TKIs and targeted therapies, the role of transplantation is being re-evaluated, especially in patients who achieve sustained deep molecular responses with drug therapy [8].

Monitoring minimal residual disease (MRD) is essential to guide treatment in Ph+ ALL. Detectable levels of MRD after induction are associated with increased risk of relapse, underscoring the importance of therapeutic strategies that achieve MRD-negativity [9].

The management of Ph+ ALL has advanced significantly with the introduction of TKIs and targeted therapies. The choice of TKI, consideration of chemotherapy-free regimens, and evaluation of the role of allogeneic transplantation should be individualized, based on patient characteristics, response to treatment, and MRD monitoring. Continued research and clinical trials will be critical to optimize therapeutic strategies and improve outcomes in this challenging disease [9].

Conclusion

In conclusion, this case of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) highlights the clinical and therapeutic challenges faced by patients diagnosed with this aggressive variant of leukemia. Despite significant advances in management using tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, and bosutinib, the patient showed a complex clinical course, characterized by treatment resistance and progression to an acute phase with massive infiltration of blasts.

Case management was limited by factors such as the patient's refusal to undergo intensive chemotherapy and lack of access to allogeneic stem cell transplantation in Honduras, an intervention that might have offered greater chances of sustained remission. Hematologic complications, such as febrile neutropenia and severe anemia, further exacerbated clinical deterioration, underscoring the importance of close monitoring and a comprehensive approach in the management of these patients.

This case also highlights the need for equitable access to advanced therapies and the infrastructure needed to implement treatments such as allogeneic transplantation. Regular monitoring with molecular (Philadelphia chromosome) and minimal residual disease (MRD) studies was crucial to assess treatment response and adjust therapeutic strategies. Ultimately, this case reinforces the importance of personalizing treatment to individual patient characteristics, combining advances in targeted therapy with an approach focused on the specific limitations and needs of the setting. Case management was limited by factors such as the patient's refusal to undergo intensive chemotherapy which delayed the initiation of early treatment.

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