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Lymphoid Blast Crisis in Chronic Myeloid Leukemia: Transformation to B cell Acute Lymphoblastic Leukemia

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Abstract

Background: Chronic myeloid leukemia (CML) is driven by the BCR-ABL1 fusion oncoprotein and is usually controllable with first- and second-generation tyrosine-kinase inhibitors (TKIs). However, ~5–7 % of patients eventually develop blast crisis, and a minority of these transform to B cell acute lymphoblastic leukemia (ALL-B), a biologically aggressive state with a median overall survival of only 6–12 months despite therapy. Third-generation TKIs such as ponatinib, as well as antibody-based or cellular therapies (e.g., blinatumomab, inotuzumab ozogamicin, CAR-T), are emerging as potential options for refractory lymphoid blast crisis.

Case presentation: A 38-year-old man with a 10-year history of CML on sequential imatinib then nilotinib presented with progressive fatigue, bleeding, and fever. Laboratory studies demonstrated leukocytosis with 86% blasts, severe anemia, and thrombocytopenia. Bone-marrow examination confirmed lymphoid transformation; flow cytometry revealed $CD34^{+}CD19^{+}CD79a^{+}$ blasts with aberrant CD13/CD33. BCR-ABL1-kinase domain sequencing showed no T315I mutation, yet clinical resistance to both TKIs was evident. Cytoreduction with hydroxyurea provided transient benefit. Given poor performance status and infection risk, LALA chemotherapy was proposed as a tolerable, stem-cell-transplant–bridging regimen; however, the patient elected for home-based palliative care and died one week after discharge.

Conclusion: CML transformation to ALL-B poses formidable diagnostic and therapeutic challenges and carries a dismal prognosis with a less than 20% five-year survival. LALA chemotherapy may be a reasonable option in patients who are clinically vulnerable or immunocompromised. Timely recognition of disease transformation and early referral for potentially curative interventions such as stem cell transplantation are essential in managing high-risk CML. Future directions include integrating ponatinib or other novel TKIs with immunotherapeutic approaches to improve outcomes in lymphoid blast crisis.

Keywords: Chronic myeloid leukemia, Blast crisis, B cell acute lymphoblastic leukemia, Byrosine kinase inhibitor resistance, LALA chemotherapy

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the reciprocal translocation *t*(9;22)(q34;q11) that creates the BCR-ABL1 fusion oncoprotein driving uncontrolled myeloid proliferation [1]. Current epidemiologic estimates place the global, age-standardized incidence of CML at approximately 0.87 cases per 100,000 inhabitants per year, with country-specific rates ranging from 0.4 to 1.75 per 100,000. CML accounts for roughly 15% of adult leukemias and shows a modest male predominance (male–female ratio 1.2–1.7) with a median diagnostic age of ≈56 years [2].

Epidemiology in Asia shows a distinct pattern, with both lower crude incidence and a younger median age of onset (36–55 years) compared with Western cohorts [3]. A recent Indonesian single-center series reported a mean age of 39 years at diagnosis, underscoring this regional difference [4].

CML progresses through three distinct clinical phases: chronic phase (CP), accelerated phase (AP), and blast crisis (BC). Approximately 85% of patients are diagnosed in the chronic phase, which is typically indolent and responsive to therapy. The accelerated phase is characterized by impaired neutrophil differentiation and emerging resistance to treatment, while the blast crisis phase resembles acute leukemia, with uncontrolled proliferation of immature blasts of either myeloid or lymphoid origin [5]. Historically, in the absence of effective treatment, nearly all CP-CML cases progressed to BC within 3 to 5 years. However, with the advent of tyrosine kinase inhibitors (TKIs), such transformation has become rare. Long-term follow-up data from the IRIS trial showed that the 10-year risk of progression to blast phase with imatinib therapy was approximately 6.9% [6]. Within all blast transformations, 20-30% fall into lymphoid lineage [7].

Currently, five TKIs are approved for the treatment of CML: imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. The first four are approved for first-line therapy by major regulatory agencies, including the FDA and EMA [8]. While these agents have significantly improved survival outcomes, resistance remains a notable challenge, affecting 20–30% of patients [9]. The most frequent mechanism involves point mutations in the ABL1 kinase domain that reduce the binding affinity of TKIs, often through conformational changes in the BCR-ABL1 oncoprotein. Over 100 such mutations have been identified and are categorized into five main groups: (I) phosphate-binding loop (P-loop), (II) drug contact site, (III) catalytic (C-loop), (IV) activation loop (A-loop), and (V) myristate pocket [10]. Among these, P-loop mutations, such as Y253F/H and E255K/V, are the most prevalent, accounting for 36–48% of resistant cases and are associated with higher rates of disease progression. The T315I mutation, located in the drug-binding site, is particularly significant as it confers resistance to all TKIs except ponatinib [11,12].

In addition to kinase domain mutations, resistance may result from BCR-ABL1 overexpression, aberrant drug transporter function, activation of alternative oncogenic pathways, genomic instability, epigenetic modifications, leukemic stem cell persistence, and immune evasion [12-14].

Here, we report a case of TKI-resistant CML that evolved into ALL-B and discuss diagnostic and therapeutic challenges in light of current literature. A case of TKI-resistant CML that evolved into ALL-B and discuss diagnostic and therapeutic challenges in light of current literature.

Case Presentation

A 38-year-old male entrepreneur, diagnosed with CML at age 28, initially achieved complete hematologic response on imatinib 400 mg/day. After eight years, rising BCR-ABL1 transcript levels (18%) and recurrent febrile episodes prompted escalation to nilotinib 600 mg/day. Follow-up revealed further molecular relapse (73.7%), progressive splenomegaly, and transfusion-dependent cytopenias. Despite ongoing nilotinib therapy, he required repeated hospital admissions for febrile episodes, persistent headaches, and bleeding manifestations.

He then presented to the ED in September 2024 with progressive generalized weakness, remittent fever, headaches, along with gum bleeding and melena. Vital signs were stable (BP 110/70 mmHg; HR 96 bpm; T 37.8 °C). Conjunctival pallor, sub-icteric sclerae, hepatomegaly, and Schuffner grade-3 splenomegaly were noted. Eastern Cooperative Oncology Group (ECOG) performance status was 2.

Complete blood count showed hemoglobin 6.6 g/dL, white-cell count 274×10^9/L with 86% blasts, and platelets 17×10^9/L. Peripheral smear demonstrated marked leukocytosis with 54% myeloblasts, anisopoikilocytosis, and teardrop cells. Bone-marrow aspirate was a dry tap; biopsy revealed hypercellularity with >30% lymphoid blasts. Flow cytometry confirmed $CD34^+CD19^+CD79a^+HLA\text{-}DR^+$ blasts co-expressing CD13/CD33, consistent with ALL-B. Reverse-transcriptase PCR detected BCR-ABL1 (p210) transcripts; kinase-domain sequencing showed no T315I mutation.

Supportive care included transfusions and cytoreduction with hydroxyurea 1 g twice daily. Despite supportive measures, the patient's condition continued to deteriorate, and he subsequently developed hospital-acquired pneumonia. After a multidisciplinary discussion, LALA chemotherapy was selected as the most feasible induction regimen because access to allogeneic hematopoietic stem-cell transplantation was severely constrained at our center. However, the patient declined intensive therapy and opted for palliative management at home.

The patient was discharged with home-based supportive care and died seven days later due to progressive disease and sepsis.

Discussion

Chronic myeloid leukemia (CML) is driven by constitutive BCR-ABL1 kinase activity that confers unchecked proliferation and genomic instability. While first- and second-generation tyrosine-kinase inhibitors (TKIs) deliver durable remission for most patients, clonal evolution—through BCR-ABL1 kinase-domain mutations, gene amplification, or cooperating lesions in factors such as *IKZF1* and *CDKN2A/B*—remains the substrate for progression to blast crisis, reported in fewer than 10% of contemporary series [8,9]. Lymphoid blast crisis, particularly lineage switch to B-cell acute lymphoblastic leukemia (ALL-B) as in our patient, is uncommon yet carries the poorest outlook, with median survival typically <12 months.

This patient showed transformation of CML chronic phase, which progressed into blast phase, and later to acute B lymphoblastic leukemia. The transformation of chronic

myeloid leukemia (CML) into B-cell acute lymphoblastic leukemia (ALL-B), although less common than myeloid blast crisis, is a recognized form of disease progression, particularly during blast phase. This phenomenon is primarily attributed to the pluripotent nature of the original leukemic stem cell, which retains the capacity for both myeloid and lymphoid differentiation. Under selective pressure, such as tyrosine kinase inhibitor (TKI) therapy, pre-existing lymphoid-primed subclones may expand, leading to a lineage switch and the emergence of a dominant lymphoid phenotype. This transformation is often driven by the accumulation of secondary genetic abnormalities in addition to the *BCR-ABL1* fusion gene, such as deletions of *IKZF1*, *CDKN2A/B*, and mutations in *PAX5*, which are also commonly observed in *de novo* B-ALL and are associated with impaired lymphoid differentiation and increased proliferative capacity [15].

Furthermore, the constitutive tyrosine kinase activity of BCR-ABL1 promotes genomic instability, facilitating clonal evolution and the acquisition of mutations that contribute to leukemic transformation. Epigenetic dysregulation, such as aberrant DNA methylation or histone modifications, may also silence tumor suppressor genes and support lineage reprogramming [15,16]. Clinically, lymphoid blast transformation may present with extramedullary involvement and is frequently associated with resistance to standard TKI therapy, particularly in the presence of mutations like T315I [17]. These transformations typically confer a poorer prognosis and often require intensified treatment strategies, including chemotherapy and consideration of allogeneic hematopoietic stem cell transplantation [16,18].

Emerging therapies for TKI-resistant CML lymphoid blast crisis fall into two broad categories. First, next-generation TKIs that bind outside the traditional ATP site, most notably asciminib, an allosteric STAMP inhibitor, are producing deep molecular responses even after multiple prior TKIs. A phase I dose-finding study that combined asciminib with dasatinib and prednisone in Ph+ ALL/LBC achieved MR4.5 in >70% of evaluable patients and is being expanded internationally [19]. Third-generation agents designed to overcome T315I are also advancing: olverembatinib (HQP1351) has shown a 68% major hematologic response rate in relapsed Ph+ ALL/LBC, including T315I-positive cases, while vodobatinib (K0706) is yielding durable cytogenetic remissions in heavily pre-treated CML cohorts, with a dedicated blast-phase stratum in its ongoing phase II programme [20,21]. These trials collectively support earlier molecular profiling and rapid access to mutation-specific TKIs before irreversible clonal evolution occurs.

Second, immune-based and chemotherapy-free combinations are surfacing as therapy alternatives. The ponatinib–blinatumomab regimen, tested in a single-arm phase II study of relapsed/refractory Ph+ ALL and CML lymphoid blast phase, produced 83% MRD-negative complete remissions with minimal myelosuppression [22]. Antibody–drug conjugates are also being integrated: a phase I/II trial pairing inotuzumab ozogamicin with bosutinib reported a 75% complete-response rate and manageable hepatotoxicity in patients lacking T315I [23]. Finally, early multicenter experience with CD19-directed CAR-T cells in CML-LBC has documented molecular remissions in otherwise refractory disease, highlighting a potential bridge or alternative to allo-HSCT for selected patients [24]. Incorporating these investigational modalities into risk-adapted algorithms—preferably within clinical trials—offers a realistic avenue to improve the historically poor <12-month survival associated with ALL-B transformation.

Loss of response to sequential TKIs in the absence of the gatekeeper T315I mutation, as observed here, underscores that resistance can also arise from BCR-ABL1 over-expression, aberrant drug-transport mechanisms, and off-target genomic alterations [10,15]. Once lymphoid transformation occurs, standard CML-directed TKI monotherapy is inadequate. Current consensus advocates ALL-style multi-agent chemotherapy, most commonly Hyper-CVAD, paired with a potent, mutation-directed TKI such as ponatinib; this approach achieves complete remission in roughly 50–70% of cases and provides the bridge to allogeneic hematopoietic stem-cell transplantation (allo-HSCT), the only consolidative therapy with curative potential [17]. In the case of our 38-year-old patient with marked splenomegaly, recurrent febrile and bleeding episodes, and a history of hospital-acquired infection signaled heightened vulnerability to severe myelosuppression and sepsis. Hyper-CVAD was therefore deemed unsuitable because it is associated with deeper cytopenias and prolonged hospitalization [17]. A LALA-based induction regimen, administered alongside ongoing TKI therapy, offered a more favorable efficacy–toxicity balance in our resource-limited setting and preserved the option of subsequent allogeneic stem-cell transplantation. This choice illustrates the importance of tailoring therapy not only to disease biology but also to individual comorbidity and treatment-related risk [25].

Despite therapeutic advances, the prognosis after lymphoid blast crisis is still guarded. Meticulous molecular monitoring, rapid mutation profiling, and expedited referral for allo-HSCT are therefore critical. Contemporary series show that proceeding to transplant during the first morphologic or MRD-negative remission, ideally within 3–4 months of achieving response and within the first year after blast-phase diagnosis, can double 3-year overall survival compared to when transplantation is delayed or omitted (~55% vs <25%). International guidelines therefore recommend that donor search and conditioning work-up begin as soon as lymphoid transformation is confirmed, with bridging therapy (e.g., Hyper-CVAD ± ponatinib, ponatinib–blinatumomab, or asciminib-based regimens) used to attain a transplantable remission and to keep disease burden minimal until engraftment [26,27].

For patients who are transplant-ineligible, owing to comorbidity, frailty, donor unavailability, or personal

preference, early integration of palliative care is essential. Key components include proactive symptom control (analgesia for bone pain, antiemetics, and dyspnea support), transfusion and infection prophylaxis protocols, psychological and spiritual counselling, and advance-care planning that aligns therapy intensity with the patient's goals. Low-intensity disease-modifying options (single-agent TKIs, blinatumomab maintenance, or oral corticosteroid-based regimens) can confer cytoreduction while preserving quality of life, but they should be framed within a realistic discussion of limited long-term disease control. Embedding palliative services from diagnosis of blast crisis ensures that clinical optimism about curative strategies is balanced with compassionate, patient-centered decision-making [28].

Conclusion

Lineage switch of CML to ALL-B is uncommon yet clinically devastating. Timely recognition, comprehensive genotyping, and integration of targeted TKIs with lymphoid-directed chemotherapy followed by allo-HSCT offer the best prospect for prolonged survival. In patients with poor performance status, LALA chemotherapy provides a feasible bridge while respecting quality-of-life considerations.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions Statement

MF collected clinical data and drafted the manuscript. LMJ and JD supervised case management, contributed to the literature review, and critically revised the manuscript. All authors approved the final version.

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