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Case Report

Efficacy and Safety of Flumatinib for Maintenance Therapy in Ph-Positive B-Cell Acute Lymphocytic Leukemia Patients with Insensitivity or Intolerance to Dasatinib after Allogeneic Hematopoietic Stem Cell Transplantation: Two Case Reports

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Received: 11 May 2024; Accepted: 27 June 2024; Available online: 30 December 2024

ABSTRACT: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) presents a potential remedy for Philadelphia chromosome-positive (Ph-positive) B-cell acute lymphoblastic leukemia (B-ALL). A tyrosine kinase inhibitor (TKI), such as dasatinib, may decrease the incidence of leukemic relapse during post-transplantation maintenance therapy. However, resistance or intolerance to TKIs remains a major challenge. The paper presented the clinical data of two patients with Ph-positive B-ALL who were treated with flumatinib after allo-HSCT. This case report aims to evaluate the safety and efficacy of flumatinib, a selective BCR/ABL inhibitor, in treating Ph-positive B-ALL patients who show resistance or intolerance to dasatinib after allo-HSCT. The two Ph-positive B-ALL patients treated with flumatinib following allo-HSCT tolerated the medication well and achieved sustained molecular remission. The paper suggests that flumatinib exhibit significant efficacy and safety in patients with Ph-positive B-ALL who underwent allo-HSCT, which deserves additional investigation.

Keywords: Acute lymphoblastic leukemia; Flumatinib; Tyrosine kinase inhibitor; Allogeneic hematopoietic stem cell transplantation

1. Introduction

Acute lymphoblastic leukemia (ALL) is a prevalent form of acute leukemia in adults, accounting for 20%–30% of the total. Patients who achieve complete remission (CR) following intensive therapy consolidation may undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. Several studies demonstrated that prompt administration of tyrosine kinase inhibitors (TKIs) subsequent to transplantation can effectively avert leukemia relapse, and dasatinib exerts a potent inhibitory impact on the unmutated *BCR/ABL* gene [2]. However, the inadequate tolerability of patients following allo-HSCT restricts the clinical application of dasatinib. This paper aims to investigate the safety and efficacy of oral flumatinib maintenance therapy for ALL patients who have undergone allo-HSCT. To ascertain the efficacy and safety of flumatinib in this context, the study retrospectively analyzed clinical data from two patients diagnosed with ALL.

https://doi.org/10.70322/BG20240210009

2. Case Presentation

2.1. Case 1

The 46-year-old female was diagnosed with B-cell acute lymphocytic leukemia (B-ALL) in August 2021, characterized by *BCR/ABL P190* positive and a substantial *IKZF1* gene deletion. Her chromosomal karyotype was 45, XX, -7, t(9;22)(q34;q11). The initial treatment with dasatinib combined with a VP (vincristine plus prednisone) chemotherapy regimen resulted in CR, confirmed by bone marrow smear analysis. During the post-remission phase, she received a second course of chemotherapy, which included dasatinib, a VP regimen, and an additional dose of vincristine. Based on subsequent bone marrow smear analysis, which showed no residual disease and conversion to a negative fusion gene status, CR persisted. On 23 November 2021, the patient underwent allo-HSCT from her son, who was a 5/10 match and shared the same O blood type. She did not experience any reported adverse effects when receiving dasatinib 100 mg once daily in conjunction with chemotherapy throughout the pre-transplantation phase. She was continued on maintenance therapy with dasatinib 50 mg once daily following transplantation. However, three months after transplantation, she developed bilateral lower extremity edema, scleral hemorrhage, and complete cytopenia, which were suspected to be associated with dasatinib therapy. These symptoms improved after she was switched to flumatinib 200 mg once daily. Currently, one-year post-transplantation, she continues to test negative for minimal residual disease (MRD).

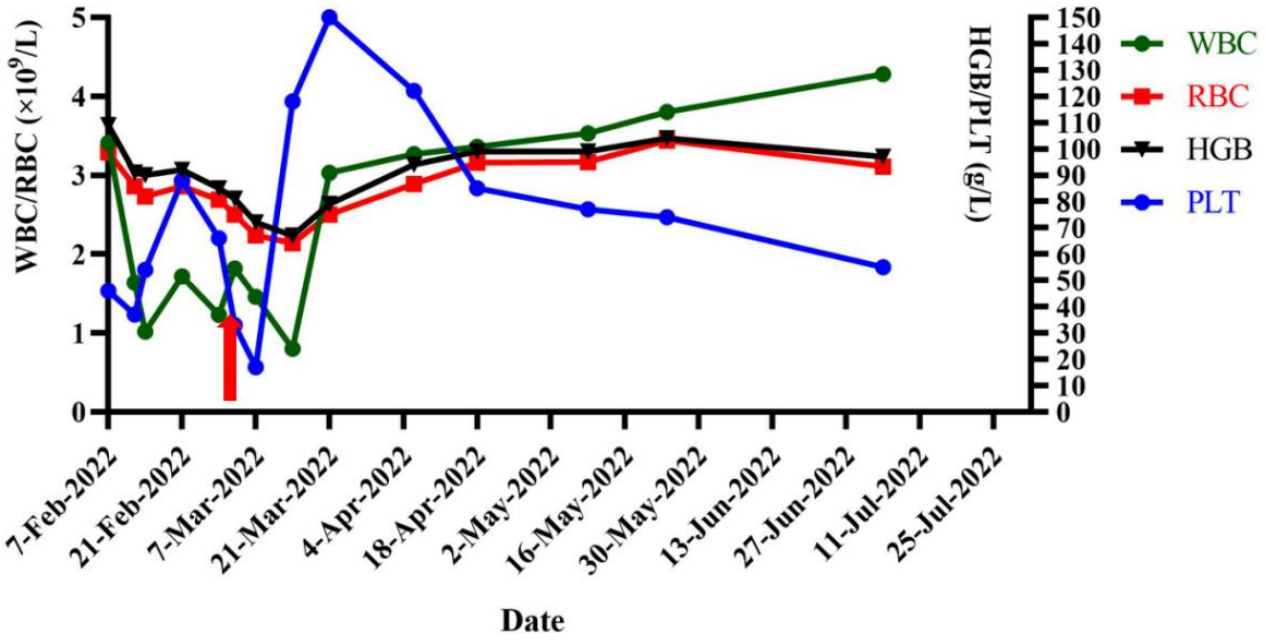
2.2. Case 2

The 47-year-old male presented with a cough, as the main complaint was discovered to have elevated white blood cell (WBC) counts in October 2020. Peripheral blood examination revealed the presence of 90% blast cells. Bone marrow morphological examination indicated acute leukemia, with a biopsy confirming B-ALL or B-cell lymphoma. Immunophenotypic analysis identified malignant B-lineage precursor cells, comprising approximately 92.8% of nucleated cells. The patient tested positive for the *BCR/ABL P210* fusion gene, and chromosomal karyotype analysis revealed a 46, XY, t(9;22)(q34;q11.2) translocation. He was diagnosed with ALL (*BCR/ABL P210* positive) and received chemotherapy with a combination of dasatinib and VD (vincristine plus dexamethasone) regimen. Despite multiple tests, the fusion gene remained positive, with the *BCR/ABL P210* fusion gene last quantified prior to transplantation at 0.0470%. On 28 April 2021, an allo-HSCT was performed with the patient's daughter as a 7/12 compatible donor, both having B+ blood type. He received a daily dose of dasatinib 100 mg combined with chemotherapy before transplantation but failed to attain molecular remission, as evidenced by the persistence of the *BCR/ABL* fusion gene. After allo-HSCT, he achieved MRD negative and gene conversion to negative status. He began maintenance therapy with flumatinib 200 mg once daily in the fifth month after transplantation and has remained disease-free for the past two years.

3. Discussion

Developed in China, flumatinib is a small molecule TKI that exhibits a stronger inhibitory effect on intracellular *BCR/ABL* tyrosine kinase activity compared to imatinib [3]. For the patients who received TKI combined with chemotherapy treatment and obtained complete molecular remission (CMR) within 3 months, allo-HSCT can achieve similar therapeutic effects as late sequential autologous stem cell transplantation [4]. Flumatinib also showed a good effect on promoting the negative conversion of MRD [5].

Dasatinib was administered to Case 1 following transplantation. However, the patient experienced significant fluctuations in blood hemogram and severe adverse effects. In contrast, after switching to flumatinib, the patient's blood hemogram stabilized over time with fewer fluctuations and no further discomfort (Figure 1). As seen in Figures 2 and 3, after switching to flumatinib, the patient's hepatic and renal function gradually improved, indicating that flumatinib offered lower, more manageable adverse effects and was safer for ALL patients following allo-HSCT. However, in Case 2, the patient received oral dasatinib prior to transplantation but did not achieve molecular remission of the *BCR/ABL* fusion gene. The patient was maintained on oral flumatinib for 5 months after transplantation and was followed up closely at our outpatient clinic.



Figrue 1. Comparison before and after oral administration of dasatinib and flumatinib in Case 1. Case 1 started oral administration of dasatinib on 7 February 2022 and switched to flumatinib on 3 March 2022. The left Y-axis represented white blood cells (WBC) and red blood cell (RBC) counts, and the right Y-axis represented hemoglobin (HGB) and platelet (PLT) counts.

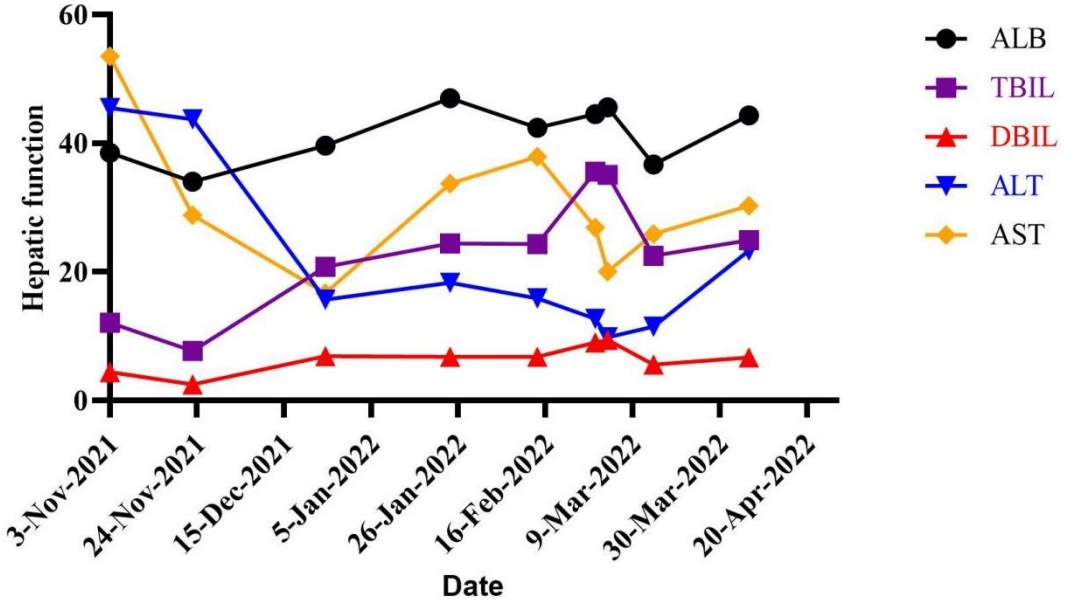


Figure 2. Changes in hepatic function over time during treatment in Case 1.

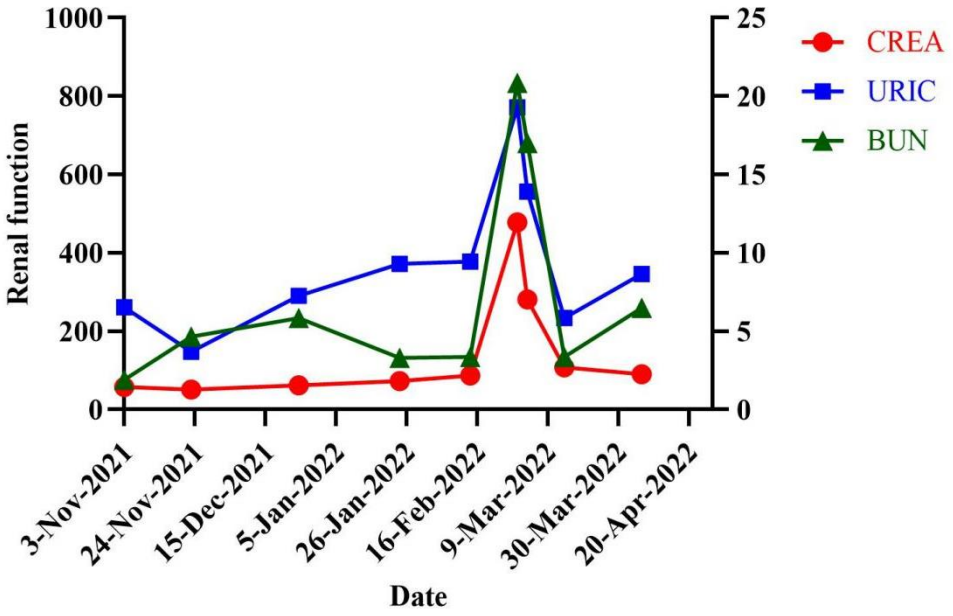


Figure 3. Changes in renal function over time during treatment in Case 1.

Studies showed that ponatinib inhibits tyrosine kinases better than first-generation and second-generation TKIs [6]. And ponatinib was probably driven by the higher CR with this regimen compared with dasatinib. However, ponatinib is not currently available in China. Flumatinib had considerable efficacy in patients with Ph-positive ALL in terms of inducing a negative conversion of MRD and remission rate [5]. A meta-analysis suggested that in patients with chronic myeloid leukemia, flumatinib had a higher 3-month early molecular response and 1-year progression-free survival than nilotinib, dasatinib, and imatinib, as well as a lower incidence of severe adverse reactions and comparable efficacy to other second-generation TKIs [7].

Li Chenxi's team confirmed that there was a difference in the 2-year disease-free survival (DFS) rate and overall survival (OS) rate between flumatinib and imatinib. The second-generation TKIs combined chemotherapy could significantly improve CR and complete remission quality of Ph+ ALL, and the clinical efficacy of flumatinib was similar to other second-generation TKIs combined chemotherapy [3].

In summary, these two cases suggest the efficacy and safety of flumatinib in treating Ph-positive B-ALL patients who are insensitive or intolerant to dasatinib after allo-HSCT. The patients' blood hemograms steadily recovered, showing fewer fluctuations and no further discomfort, making flumatinib an ideal drug choice for ALL patients post-allo-HSCT. However, due to the small number of clinical cases in this investigation, further validation is urgently needed. This underscores the necessity for additional multicenter trials and long-term follow-up in future research.

Acknowledgments

We would like to thank all those who gave us thoughtful advice on graph editing, data collection, and language editing.

Author Contributions

K.C. and S.Z. obtained and analyzed the clinical data. G.H. and Y.D. created the charts, and K.C. revised the chart details. The authors were involved in caring for patients, editing charts, and writing and revising the manuscript. S.L., Y.S., and H.Y. reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Ethics Statement

Involving human participants was approved by the Ethics Committee of the General Hospital of Western Theater Command, People's Liberation Army. All methods were carried out in accordance with the guidelines of the Declaration of Helsinki.

Informed Consent Statement

The patients provided written informed consent to participate in this study.

Funding

This research received no external funding.

Declaration of Competing Interest

The authors declared no conflict of interests.

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