

Case Report

The First Reported Case of Allogenic Hematopoietic Stem Cell Transplantation for CML Blast Phase (Monocytic Lineage) in the Tyrosine Kinase Inhibitor Era

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Keywords

Chronic myeloid leukemia · Chronic myeloid leukemia blast phase (monocytic lineage) · Tyrosine kinase inhibitor · Hematopoietic stem cell transplantation · Hyper-acute graft-versus-host disease

Abstract

Chronic myeloid leukemia (CML) blast phase (monocytic lineage) is extremely rare. A 39-year-old Japanese man was diagnosed with CML blast phase (monocytic lineage). T315I mutation was positive, ponatinib was initially started, and then, allogenic hematopoietic stem cell transplantation (allo-HSCT) was performed. Seven days after allo-HSCT, hyper-acute graft-versus-host disease developed, and medial temporal lobe encephalitis emerged 24 days after allo-HSCT. He was alive for over 1 year after allo-HSCT. This is the first case report of HSCT for CML blast phase (monocytic lineage) in tyrosine kinase inhibitor era. Further cases should be documented for effective treatment regimen and analysis of clinical features.

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Published by S. Karger AG, Basel

Introduction

Since the use of tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML) blast phase has become uncommon [1]. Blast phase (myeloid lineage) accounts for two-thirds of cases of blast phase, followed by B lymphoid lineage and megakaryocytic lineage; blast phase (monocytic lineage) is extremely rare [2]. In general, the prognosis of CML blast phase is poor. Herein, we report a case of allogeneic hematopoietic stem cell transplantation in a patient with an extremely rare CML blast phase (monocytic lineage), who survived for more than 1 year thereafter.

Case Report/Case Presentation

The patient was a 39-year-old Japanese male who was previously healthy, had no allergies, and was not on any medications. He visited his regular doctor because of persistent general malaise and fever for more than 1 month. The patient had a hepatosplenomegaly, weight loss, leukocytosis, elevated lactate dehydrogenase, and a positive BCR/ABL on fluorescent in situ hybridization of the peripheral blood. He was diagnosed with CML and therapy with the TKI, dasatinib, was initiated. However, dasatinib treatment was discontinued due to gastrointestinal bleeding, and the patient was referred to our hospital for further treatment.

Laboratory data at the time of the first visit were as follows: white blood cell count, 8,900/ μL (blast cells, 1.0%; myelocytes, 1.0%; metamyelocytes, 1.0%; neutrophils, 22.0%; lymphocytes, 13.0%; and monocytes, 62.0%); red blood cell count, $398 \times 10^4/\mu\text{L}$; hemoglobin, 11.8 g/dL; hematocrit, 35.9%; mean corpuscular volume, 90.2 fL; platelet count, $3.3 \times 10^4/\mu\text{L}$; reticulocyte count, 19.0‰; lactate dehydrogenase, 263 U/L (reference, 120–220 U/L); BCR/ABL1 (fluorescent in situ hybridization), 88.0% positive; major BCR-ABL1 mRNA (International Scale [IS]), 73.3579%, and T315I mutation-positive.

Figure 1a, b show myeloscopic images, blast count was 22.4% and monocyte 38.8%. Flow cytometry (Fig. 1c) shows blast count 11.0% and monocyte 39.6%. Chromosome analysis (Fig. 1d) shows various abnormalities addition to t(9; 22). Based on these results, the patient was diagnosed with CML blast phase (monocytic lineage). As the patient was positive for the T315I mutation, debulking with ponatinib was performed, and early allogeneic transplantation was planned.

Figure 2a shows the clinical course of transplantation. Ponatinib was continued until day -8, and conditioning (total-body irradiation, 3 Gy/day for 4 days; cyclophosphamide, 60 mg/kg/day for 2 days) was started from day -7. Umbilical cord blood was human leukocyte 4/6 antigen matched (B, DR 1 locus mismatched), and with a cluster of differentiation 34 positive cell count of 0.62×10^5 cells/kg was used for transplantation. Graft-versus-host disease (GVHD) prophylaxis consisting of tacrolimus and mycophenolate mofetil was given. The patient's performance status was 0, and hematopoietic cell transplantation-comorbidity index was 0. On day 7 after transplantation, the patient developed a systemic (>50%) skin rash, fever $>40^\circ\text{C}$, liver damage (marked increase in aspartate aminotransferase and alanine aminotransferase), and a decrease in SpO_2 , suggesting hyper-acute GVHD. On day 24, he experienced impaired consciousness. (Figure 2b) shows cerebral magnetic resonance imaging fluid-attenuated inversion recovery images and (Fig. 2c) shows diffusion-weighted images obtained at that time. Both images showed high signal intensity in the medial temporal lobe, suggesting characteristic of encephalitis. His IS was 0.0075% on day 57, and hence, ponatinib was resumed. The patient was discharged from the hospital on day 233. Although the IS value gradually increased thereafter, the patient was still alive 1 year after allogeneic transplantation.

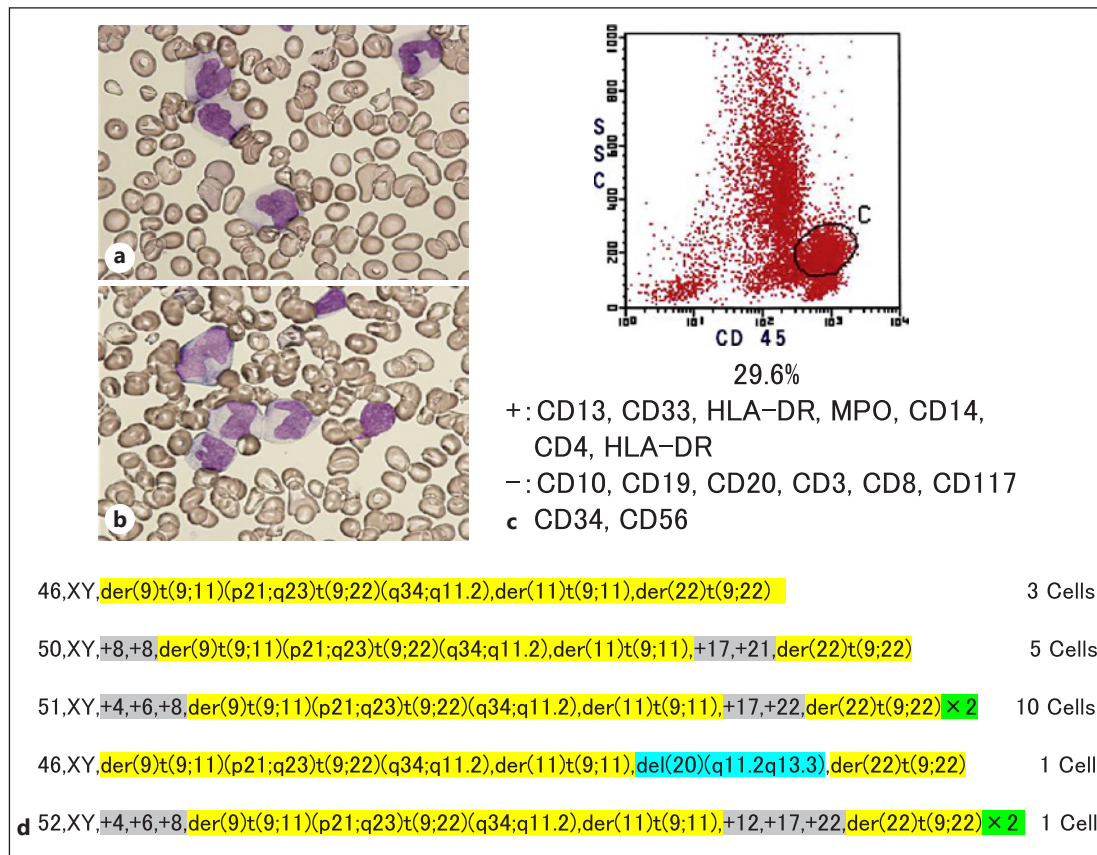


Fig. 1. Bone marrow test results. **a, b** Smears show 38.8% of monocytes with cleaved nuclei and gray cytoplasm. **c** On FCM, the monocyte fraction accounted for 29.6%, CD34 and CD117 were negative, and MPO and CD14 were positive. **d** Chromosome analysis showed *t*(9;22), as well as additional chromosomal abnormalities: *t*(9;11), *del*(20), and double Ph. Abbreviations: FCM, flow cytometry; CD, cluster of differentiation, MPO, myeloperoxidase.

Discussion/Conclusion

There have been 13 previous reports of CML blast phase (monocytic lineage) in the English-language literature [3, 4]. However, there are only two reports of CML blast phase (monocytic lineage) in the TKI era.

In our patient, chromosome analysis (Fig. 1d) showed multiple chromosomal abnormalities in addition to *t*(9;22), which is present in more than 90% of patients with CML. *t*(9;11), deletion of the long arm chromosome 20 (*del*[20q]), Philadelphia chromosome duplication, trisomy and tetrasomy are characteristic findings in this case. *t*(9;11) is present in approximately 5% of adults and almost 15% of children with AML [5]. AML with this translocation is often classified as M4 or M5 in the FAB classification, and is considered an independent disease, “AML with *MLL3-KMT2A*,” according to the revised World Health Organization classification of 2017. *del*(20q) is detected in 4–10% of myelodysplastic syndromes [6]. There is also a report of chronic myelomonocytic leukemia with *del*(20q) [7]. However, it is unclear whether these chromosomal abnormalities are common in CML blast phase (monocytic lineage) or were only present in the present case. Additional chromosomal abnormalities and Philadelphia chromosome duplication are frequent findings in CML blast phase (monocytic lineage).

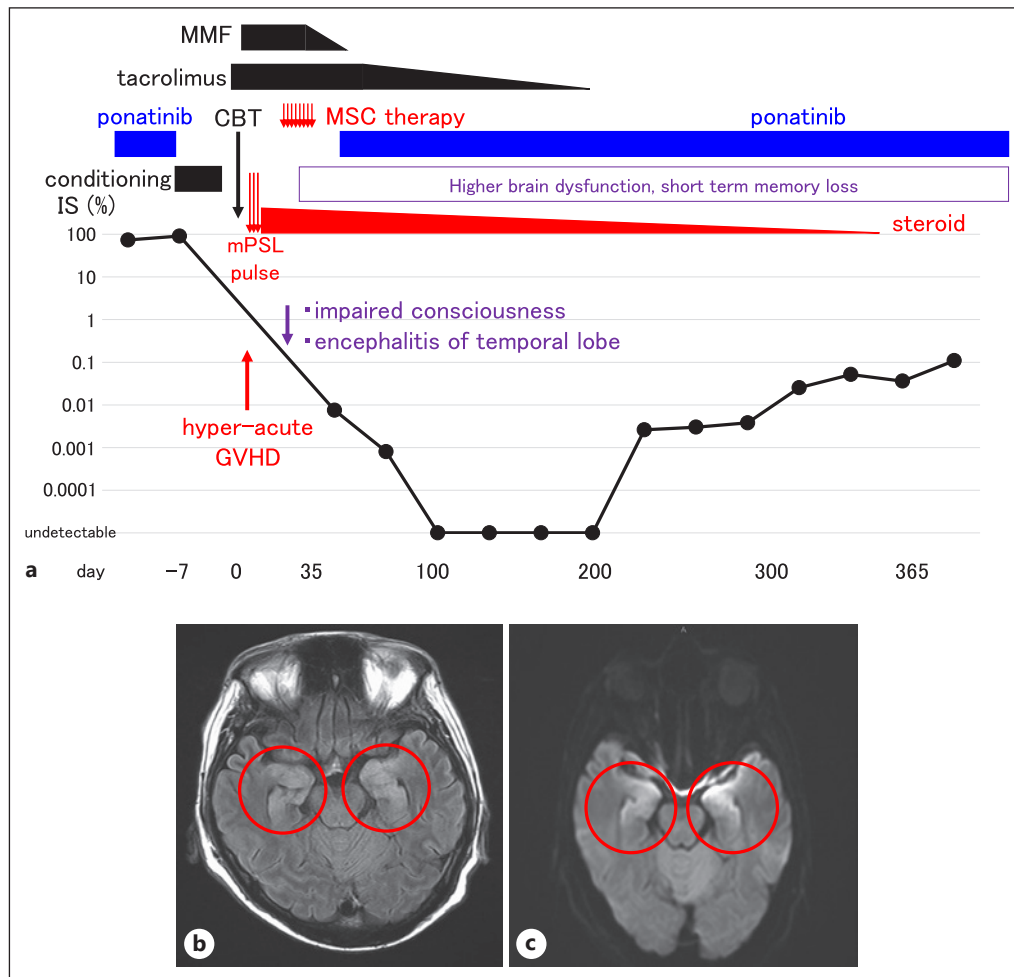


Fig. 2. Clinical course of transplantation. **a** IS(%) of BCR/ABL trend, pretransplant treatment, GVHD prophylaxis, GVHD treatment, and symptoms during the course of transplant. **b** FLAIR image and **(c)** diffusion-weighted image on brain MRI. In both images, there was high signal intensity in the medial temporal lobe, indicating encephalitis. Abbreviations: MMF, mycophenolate mofetil; CBT, cord blood transplantation; MSC, mesenchymal stem cell or mesenchymal stroma cell; mPSL, methylprednisolone, IS, international scale; GVHD, graft-versus-host disease; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

In this case, systemic rash, high fever, liver damage (marked increase in aspartate aminotransferase and alanine aminotransferase) and decrease in SpO₂ were observed on day 7 after transplantation, which we believe to have been due to hyper-acute GVHD. Hyper-acute GVHD is a serious complication that develops by day 14 after transplantation [8], and is characterized by systemic skin rash, high fever, diarrhea, hepatic dysfunction, pulmonary edema, and heart failure [9]. In a previous report, 55.6% of patients with juvenile myelomonocytic leukemia [10] and 33.8% of patients with AML M5 experienced acute GVHD after allogeneic transplantation [11], suggesting that the incidence of GVHD tends to be higher in patients with monocytic leukemia. Although there is no definitive information on the incidence of hyper-acute GVHD, it may be possible that the incidence of acute GVHD and hyper-acute GVHD is also high in CML blast phase (monocytic lineage).

Imatinib, dasatinib, nilotinib [12], and bosutinib [13] are reportedly ineffective in patients with T315 mutation-positive CML, and ponatinib is recommended in these patients [14].

In advanced CML, allogeneic transplantation is associated with better outcomes than single-agent TKIs [15]. Furthermore, in T315I mutation-positive CML blast phase, ponatinib alone is associated with lower overall survival at 24 and 48 months than allogeneic stem cell transplantation [16]. Since our patient had T315I mutation-positive CML blast phase (monocytic lineage), the most appropriate treatment strategy was to perform allogeneic transplantation as early as possible while achieving debulking with ponatinib.

This is the first case of allogeneic transplantation for CML blast phase (monocytic lineage) in the TKI era. Our experience suggests that allogeneic transplantation might be the most suitable treatment for CML blast phase (monocytic lineage) regardless of the presence of T315I mutation. The usefulness of allogeneic transplantation for CML blast phase (monocytic lineage) needs to be further evaluated in a larger number of patients.

This is the first case report of allogeneic transplantation for CML blast phase (monocytic lineage), which is, globally, extremely rare in the TKI era. Although long-term survival for more than 1 year was achieved in this case, analysis of a larger number of cases is desired for determination of the clinical characteristics and establishment of an appropriate treatment policy.

Acknowledgments

We thank the members of Department of Hematology, Toyama Prefectural Central Hospital and the members of Department of Hematology and Immunology, Kanazawa Medical University Hospital.

Statement of Ethics

The patient is now deceased, but written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images before his death. This study was approved by the Ethics Committee of Toyama Prefectural Central Hospital (60-31).

Conflict of Interest Statement

We have no conflicts of interest.

Funding Sources

The authors received no financial support for the authorship.

Author Contributions

Shinya Yamada and Hirokazu Okumura were attending doctors in Toyama Prefectural Central Hospital. Kotaro Arita and Shuichi Mizuta were attending doctors in Kanazawa Medical University Hospital. Shinya Yamada wrote the manuscript and Kotaro Arita, Yukio Kondo, Shuichi Mizuta and Hirokazu Okumura contributed to interpretation of data and critically revised the manuscript.

Data Availability Statement

All data needed for this manuscript are included in this article. Further inquiries can be directed to the corresponding author.

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