Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia Rescued with a Second Allogeneic Stem Cell Transplantation from a Haploidentical Mother after Relapse following Cord Blood Transplantation

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Abstract

A 32-year-old female patient who had Philadelphia chromosome–positive acute lymphoblastic leukemia underwent cord blood transplantation while in her second remission. However, she had a hematological and central nervous system relapse 3 months later. After reinduction with imatinib mesylate, unmanipulated peripheral blood stem cell transplantation was performed from the patient’s haploidentical mother with a reduced-intensity conditioning regimen. Rabbit antithymocyte globulin, tacrolimus, and methylprednisolone were used for prophylaxis of graft-versus-host disease. Engraftment of neutrophils was observed on day 12, and complete donor chimerism was obtained by day 24. The posttransplantation course was uneventful. Although the patient had a relapse 10 months later, this case demonstrated that transplantation from a haploidentical donor is clearly a feasible alternative for patients who desperately need rescue transplantation.

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Key words: Acute lymphoblastic leukemia; Philadelphia chromosome; Second stem cell transplantation; HLA-mismatched hematopoietic stem cell transplantation; Fetomaternal microchimerism; Imatinib mesylate

1. Introduction

Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) is a hematologic malignancy with very poor prognosis, and allogeneic stem cell transplantation (SCT) is considered the only potentially curative therapy [1]. However, a significant number of patients have relapses even after SCT. Not many treatment options are available for patients with Ph+ ALL who have relapses after SCT. Donor lymphocyte infusion (DLI) is effective in chronic myeloid leukemia, multiple myeloma, and possibly acute myelogenous leukemia and myelodysplastic syndrome but is considered ineffective in ALL, particularly Ph+ ALL [2]. Although imatinib mesylate has activity against Ph+ ALL [3], the duration of remission induced by this drug is limited. A second allogeneic SCT after relapse can possibly be a curative option, but there are few detailed reports of Ph+ ALL patients who received a second SCT. This case report is the first describing second SCT from a haploidentical microchimeric donor after bone marrow (BM) and central nervous system (CNS) relapse after initial SCT with cord blood in the management of Ph+ ALL.

2. Case Report

A 32-year-old woman was admitted to Kita-Fukushima Medical Center in January 2002 with fever and partial disruption of the visual field. Laboratory data on admission revealed the white blood cell count was 365 × 10^9/L with 98% blast cells; hemoglobin was 5.8 g/dL, and platelet count was 20 × 10^9/L. BM examination showed hypercellular marrow with 94% blast cells. Immunophenotypic study by flow
cytometry revealed the following phenotype: CD10+, CD19+, CD20-, CD13+, CD33+, CD34+, HLA-DR+, sIg–, CD14–. The diagnosis was acute lymphoblastic leukemia (ALL), which also expressed some myeloid antigens. Cytogenetic study showed the patient had 46,XX,t(9;22)(q23;q21) with additional complex karyotype abnormalities. Minor BCR-ABL chimeric messenger RNA (mRNA) was detected by reverse transcriptase polymerase chain reaction (RT-PCR) analysis. The patient achieved complete remission (CR) after induction therapy with the Japan Adult Leukemia Study Group ALL-97 protocol. This protocol consists of cyclophosphamide (CY), daunorubicin, vincristine (VCR), prednisolone (PSL), and l-asparaginase. In May 2002, during the third course of consolidation therapy, the patient had a relapse. Bone marrow examination showed 63% lymphoblasts. CNS involvement was diagnosed with a lumbar puncture. The patient achieved a second CR (BM blasts, 1.0%) in July 2002 with administration of imatinib mesylate (STI 571) at a daily oral dose of 400 to 600 mg for 43 days (total, 30,400 mg) combined with VCR and PSL. CNS infiltration disappeared in July after intrathecal methotrexate (MTX) therapy (4 injections total). Because she had no HLA-matched siblings, the patient was referred in August 2002 to another hospital for bone marrow transplantation (BMT) from an HLA-matched unrelated donor. Immediately before the planned date for BMT, donation was canceled. Thus cord blood transplantation (CBT) was urgently arranged and performed in September 2002, as shown in Figure 1. The cord blood (HLA: A33, 31, B44, 61, DRB1 *0802, *1302) was 1-locus mismatched to the patient (patient’s HLA; see later). Before CBT, the BM was morphologically in CR, but with a detectable level at RT-PCR analysis for minor BCR/ABL. The conditioning regimen consisted of CY 120 mg/kg and total body irradiation of 12 Gy in 6 fractions followed by infusion of \(2.67 \times 10^7\) cord blood nucleated cells/kg. She achieved an absolute neutrophil count greater than \(0.5 \times 10^9/L\) on day 23. Grade 2 skin graft-versus-host disease (GVHD) developed but responded well to corticosteroid treatment. Intrathecal administration of MTX for CNS prophylaxis was performed once before CBT and 2 times after engraftment. The patient was discharged on day 54 and subsequently received follow-up as an outpatient.

On approximately day 90 after CBT, the patient had headaches and a seizure. Cerebrospinal fluid examination revealed a cell count of 3000 mononucleated cells/\(\mu\)L, 100% of which were blast cells. BM aspiration revealed a relapse of ALL (74% blast cells) associated with tumor formation in the cerebellum detected with magnetic resonance imaging (MRI). The patient was treated again with imatinib mesylate (400 mg/d for 55 days) in combination with VCR and PSL. After this reinduction therapy, BM blasts disappeared, and fluorescence in situ hybridization analysis of marrow mononuclear cells for the fusion signal of the minor BCR-ABL gene had negative results. Cerebrospinal fluid examination showed no leukemia involvement after several courses of intrathecal MTX injections. After relapse following CBT, a second SCT is considered the only curative option. Because there was no HLA-matched donor for her in the volunteer donor registries, we considered as the last option haploidentical transplantation from a family member. The HLA profiles of the patient and her family members were as follows. The patient was A33, B44, DRB1 *1101/A31, B61, DRB1 *0802. Her father was A33, B44, DR11/A24, B61, DR15. Her mother was A3, B44, DR13/A31, B61, DR8, and a sister was A24, B61, DR 15/A31, B61, DR 8. These results indicated the father and mother had HLA 2-loci mismatched in both the graft-versus-host (GVH) and the host-versus-graft directions. The sister was HLA 3-loci mismatched in the GVH direction. PCR with sequence-specific primer typing revealed fetomaternal microchimerism...