Successful Engraftment and Durable Graft-versus-host Disease Control with Haploidentical Peripheral Blood and a Short-term Conditioning Regimen for Primary Graft Failure

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Abstract

Primary graft failure occurred after cord blood transplantation for a patient with acute lymphoblastic leukemia. The second transplantation was performed using haploidentical peripheral blood. The conditioning regimen consisted of fludarabine (day -1; 30 mg/m²), cyclophosphamide (day -1; 2,000 mg/m²), and total body irradiation (day -1; 2 Gy). The immunosuppressants contained tacrolimus, prednisolone, and rabbit antithymocyte globulin (day -3 to -2; total dose: 3.75 mg/kg). The engraftment was confirmed on day 9. Both acute and chronic graft-versus-host disease were controllable. The present regimen appears to be suitable for immediate management, fast engraftment, and the durable control of complications.

Key words: graft failure, haploidentical transplantation, cord blood transplantation

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Introduction

We often encounter graft failure (GF) after allogeneic hematopoietic cell transplantation (HCT), and this failure is a major life-threatening complication. To treat GF, a second HCT is the main rescue treatment approach (1). Although many protocols have been reported for the second HCT, including the conditioning regimen and the stem cell sources, no definitive protocol has yet to be established (2-13). We herein report a case of primary GF after cord blood transplantation (CBT) for a Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph-ALL) patient. Fast engraftment and durable graft-versus-host disease (GVHD) control was achieved using a second HCT from a haploidentical sibling donor and a short-term conditioning regimen.

Case Report

A 56-year-old man was diagnosed with Ph-ALL in February 2011. In September 2011, he underwent CBT during the first hematological complete remission of leukemia, which exhibited minimum residual disease (BCR/ABL gene transcript: 1.8×10³ copies/μg RNA). A single unit of umbilical cord blood was selected that contained mismatched human leukocyte antigens (HLA)-B and -DR in both the graft-versus-host and host-versus-graft directions; the total nuclear cell count was 2.57×10⁷ cells/kg. The absence of anti-HLA antibodies was confirmed at the start of the conditioning regimen. This conditioning regimen consisted of fludarabine (day -8 to day -4; 25 mg/m²/day), melphalan (day -3 to day -2; 70 mg/m²/day), and total body irradiation (TBI) (day -1; 3 Gy). GVHD prophylaxis included short-term methotrexate and tacrolimus. On day 29 after CBT, his white blood cell...
count did not increase and a bone marrow examination revealed full recipient chimerism with severe hypoplasia, which resulted in the diagnosis of primary GF.

To address this failure, an emergent second transplantation was designed. Peripheral blood from his sister was selected for the second graft, and this blood was mismatched in both directions for HLA-A, -B, and -DR. The absence of anti-HLA antibodies and active infection were also confirmed. The second conditioning regimen consisted of fludarabine (day -1; 30 mg/m²), cyclophosphamide (day -1; 2,000 mg/m²), and TBI (day -1; 2 Gy). In addition, the GVHD prophylaxis contained tacrolimus, prednisolone (PSL, 1 mg/kg/day), and rabbit anti-thymocyte globulin (ATG, Genzyme, day -3 to -2; total dose: 3.75 mg/kg). On day 42 after the first HCT, the second HCT was performed, with the infusion of 5.0×10⁶ CD34+ cells/kg.

The engraftment and full donor chimerism were confirmed on days 9 and 23 after the second HCT. The patient became transfusion-independent from day 33. On day 50, grade II acute GVHD with skin stage 3 developed, which subsequently resolved with an increased dose of PSL (1 mg/kg/day). However, PSL-induced psychosis subsequently occurred, although it improved with a reduction in the PSL dose. Rituximab (375 mg/m²) was administered on days 89, 111, and 118 due to an elevated Epstein-Barr virus (EBV) copy number (Figure). After 9 months, hemorrhagic cystitis with adenovirus occurred and subsequently resolved with conservative therapy. After 29 months, moderate grade chronic GVHD developed, including skin lesions and arthritis, which required low-dose PSL. No other infectious diseases, viral infections, or post-transplant lymphoproliferative disorders (PTLD) have developed since. No transcription of BCR/ABL in the bone marrow has so far been detected, and his general condition has been good in the 36 months after the second HCT.

![Figure](image.png)

**Figure.** Clinical course after transplantation. The polymerase chain reaction and chimerism (% donor) testing were performed using bone marrow samples. UCBT: umbilical cord blood transplantation, RPBHCT: related peripheral blood hematopoietic cell transplantation, PSL: prednisolone, RTX: rituximab, aGVHD: acute graft versus-host disease, WBC: white blood cells, EBV: Epstein-Barr virus, PCR: polymerase chain reaction, ND: not detected.

**Discussion**

We encountered a case of primary GF after CBT for Ph-ALL, and succeeded in achieving fast engraftment and durable GVHD control using haploidentical peripheral blood from a sibling donor and a short-term conditioning regimen. Although several protocols for treating primary GF have been reported, no standard strategy has yet been established (2-12). However, the protocol used in the present case was tolerable, provided promising immediate management, and ensured fast engraftment.

The first challenge in treating primary GF is the selection of the second graft. Fuji et al. reported that using peripheral blood for the second transplantation provided significantly faster and improved engraftment, in addition to a superior survival, compared to cord blood (2). Therefore, we selected peripheral blood from a haploidentical sibling donor.

The second challenge in treating primary GF is that no standard conditioning regimen has yet been established. Among the various potential conditioning regimens, we se-
lected a short-term conditioning regimen of fludarabine (30 mg/m²), cyclophosphamide (2 g/m²), and TBI (2 Gy). This regimen has previously been reported by Sumi et al. and Kanda et al. (3, 5), and it has been shown to be beneficial due to its highly reduced intensity, improved safety, and immediate management, which results in a high percentage of successful engraftments. In the present case, we did not observe any outstanding adverse effects until the engraftment. Given the severe bone marrow suppression and immunosuppression in the first conditioning regimen, the second short-term conditioning regimen might be sufficient to achieve engraftment even after the first CBT.

The most critical concern when performing haploidentical peripheral blood HCT is GVHD control, as it requires identifying cases with a high risk of GVHD and a strict control of the immunosuppressant. Conventional GVHD prophylaxis, which includes tacrolimus with short term methotrexate, was estimated to be insufficient to control GVHD. According to the study reported by Yoshihara et al. (6), the immunosuppressants included tacrolimus, PSL, and ATG. The dose of ATG ranged 3 to 5 mg/kg and the control of acute and chronic GVHD, or other complications was feasible. This dose is lower than that used in conventional haploidentical pre-transplant conditioning regimens (5-10 mg/kg) (14-16). A higher dose of ATG is known to induce severe immunosuppression and increase the risk of viral infections or PTLD, while a lower dose of ATG increases the risk of GVHD. Finally, we selected a combination similar to that reported by Yoshihara et al. (6), and set the total ATG dose to 3.75 mg/kg.

The present conditioning regimen is similar to those reported by Sumi et al. and Kanda et al., as the short-term conditioning regimen consists of fludarabine, cyclophosphamide, and TBI (3, 5). However, one significant difference is the stem cell source. Sumi et al. selected umbilical cord blood, whereas we selected haploidentical peripheral blood from a related donor. Another significant difference is the method of T-cell depletion. Kanda et al. used alemtuzumab (20 mg), while we used a low-dose of ATG (3.75 mg/kg). In addition, the GVHD prophylaxis was different for these three regimens. However, the optimal ATG dose or GVHD prophylaxis for haploidentical transplantation remains to be elucidated. Finally, we designed a novel salvage regimen that combined a short-term conditioning regimen with a reduced dose of ATG.

During the clinical course the patient developed grade II acute GVHD, PSL-induced psychosis, and moderate grade chronic GVHD. However, all of these adverse events were controllable, and no other complications (e.g., cytomegalovirus infection or PTLD) appeared. Moreover, the administration of rituximab as a preemptive therapy for EBV reactivation may have also helped prevent the development of PTLD and GVHD. Considering this point, it is uncertain whether a reduced ATG dose is feasible for both GVHD prophylaxis and the control of related complications. Unfortunately, we were unable to examine this further because we could not sufficiently evaluate the patient’s immunological status using cytometry to analyze lymphocyte markers.

In conclusion, we herein reported a successful second transplantation after primary GF, using haploidentical peripheral blood from a sibling donor and a short-term conditioning regimen. This regimen, which included a reduced ATG dose, appears to be suitable for immediate management, fast engraftment, and the durable control of GVHD and related complications. An increase in the number of other cases and further prospective investigations are needed in the future.

The authors state that they have no Conflict of Interest (COI).

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References


