

Successful Engraftment Following Second Cord Blood Transplantation After Graft Failure in a Child With Relapsed B-ALL

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Primary graft failure is a rare but life-threatening complication after umbilical cord blood transplantation (UCBT), especially in pediatric patients with relapsed acute lymphoblastic leukemia (ALL). Optimal salvage strategies, including conditioning regimens and donor selection for second transplantation, have not been established. This report describes the case of a 9-year-old boy with relapsed B-cell precursor ALL who developed primary graft failure following the first UCBT performed during his second complete remission. The initial transplant had used a cord blood unit with a low CD34-positive cell dose and significant human leukocyte antigen (HLA) and ABO mismatch. Despite myeloablative conditioning, neutrophil engraftment failed, and donor chimerism remained minimal. An urgent second UCBT was performed using a different cord blood unit with improved HLA compatibility and markedly higher total nucleated and CD34-positive cell doses, following reduced-intensity conditioning with fludarabine and low-dose total body irradiation. Sustained neutrophil engraftment was achieved on day +34, with stable full donor chimerism thereafter. Post-transplant complications, including hemophagocytic syndrome, sinusoidal obstruction syndrome, acute graft-versus-host disease, and viral reactivation, were successfully managed. This pediatric case demonstrates that, in the absence of a suitable donor and with prompt intervention, a second UCBT is a feasible salvage option after primary graft failure.

Key words: graft failure, second transplantation, cord blood transplantation, acute lymphoblastic leukemia

INTRODUCTION

Risk-adapted therapy has significantly improved outcomes in pediatric acute lymphoblastic leukemia (ALL), with long-term survival rates [1, 2] approaching 90%. However, relapse still occurs in approximately 10%–15% of patients, with unsatisfactory survival rates, particularly in cases of early or combined relapse [3]. Therefore, allogeneic hematopoietic stem cell transplantation (HSCT) is recommended for children with high-risk relapsed ALL who achieve a second complete remission. However, the precise indications continue to evolve in the era of immunotherapy and have thus not been established [4]. For patients lacking matched related or unrelated donors, umbilical cord blood transplantation (UCBT) is an important alternative donor source, which benefits from the immediate availability of banked units and permissive HLA mismatch [5, 6]. Since its first clinical implementation, UCBT has been performed globally across pediatric and adult populations [6, 7]. Nevertheless, UCBT remains significantly limited by delayed hematopoietic recovery and graft failure [8, 9]. Primary graft failure is associated with substantial transplant-related mortality and often requires urgent salvage transplantation. However, the optimal approach to conditioning intensity and graft source has not been established [9, 10]. Here, we describe a pediatric patient with relapsed B-cell precursor

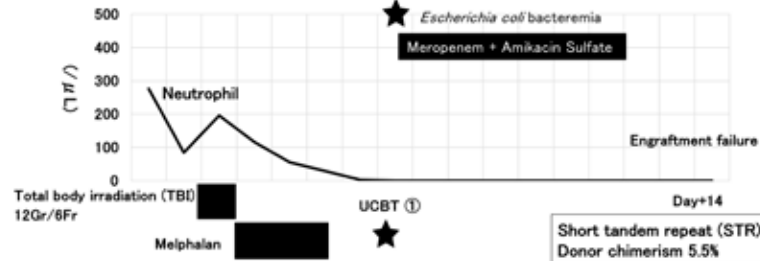
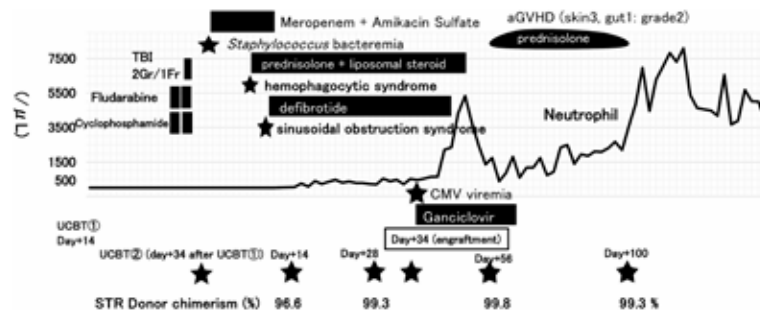
ALL who developed primary graft failure following UCBT but achieved sustained engraftment after a second UCBT.

CASE PRESENTATION

A 9-year-old boy with no significant medical history presented with headache, abdominal pain, and vomiting. Laboratory evaluation revealed pancytopenia, and bone marrow (BM) examination confirmed B-cell precursor ALL with a normal karyotype (46, XY) and no detectable fusion genes. Central nervous system (CNS) evaluation was negative at diagnosis. The patient underwent a standard-risk ALL treatment protocol (JCCG ALL-B12) and achieved complete remission. During maintenance therapy, he developed a progressive headache, vomiting, and back pain. BM revealed lymphoblast levels identical to those at the initial diagnosis. Further evaluation revealed CNS relapse with leukemic blasts detected in the cerebrospinal fluid, findings consistent with BM combined CNS relapse. The patient achieved a second complete remission following reinduction therapy consisting of inotuzumab ozogamicin, blinatumomab, and intrathecal chemotherapy. Given the high risk of relapse, HSCT was planned during the second complete remission. Myeloablative conditioning with total body irradiation (TBI) (12 Gy in six fractions) and melphalan (180 mg/m²) was administered, followed by UCBT using a

Table 1 HLA typing of the recipient and cord blood units

Locus	Recipient	First cord blood donor	Second cord blood donor
HLA-A	24:02 / 26:01	24:02 / 26:01	24:02 / -
HLA-B	07:02 / 39:01	15:01 / 54:01	07:02 / 39:01
HLA-C	07:02 / -	01:02 / 15:02	07:02 / -
HLA-DRB1	04:05 / 15:01	04:05 / 15:01	01:01 / 15:01

**Fig. 1** Clinical course associated with the first cord blood transplantation**Fig. 2** Clinical course associated with the second cord blood transplantation

cord blood unit mismatched at four of eight HLA loci (Table 1) (Fig. 1). The total nucleated cell and CD34-positive cell doses were $2.7 \times 10^7/\text{kg}$ and $0.73 \times 10^5/\text{kg}$, respectively. Donor-specific anti HLA antibodies (DSA) were not detected. After transplantation, hematopoietic recovery was not observed, and neutrophil counts failed to increase. By day +14, absolute neutrophil recovery remained absent. Short tandem repeat analysis revealed a donor chimerism rate of 5.5%. BM examination showed no evidence of donor-derived hematopoiesis. During the aplastic phase, the patient developed *Escherichia coli* bacteremia, which required treatment with broad-spectrum antibiotics. Despite adequate infection control, hematopoietic recovery did not occur. Therefore, a diagnosis of primary graft failure was made on day +28. Following the graft failure diagnosis, salvage transplantation was promptly planned. Repeat UCBT and haploidentical HSCT from a family donor were both considered as potential graft sources. However, due to scheduling constraints within the family at the time of transplantation, UCBT was ultimately selected as the graft source. For the second transplantation, reduced-intensity conditioning was administered, consisting of fludarabine ($25 \text{ mg}/\text{m}^2$) and cyclophosphamide ($750 \text{ mg}/\text{m}^2$) for 2 consecutive days, followed by low-dose TBI (2 Gy in a single fraction) (Fig. 2). UCBT was then performed using a cord blood unit with total nucleated and CD34-positive cell doses of $6.61 \times 10^7/\text{kg}$ and $4.65 \times 10^5/\text{kg}$, respectively, with 6/8 HLA matching (Table 1), reflecting both high cell doses and improved HLA compatibility. DSA

were also not detected. BM examination on day +14 revealed a donor chimerism rate of 96.6%. By day +28, donor chimerism had increased to 99.3%, and gradual hematopoietic recovery was observed. Neutrophil engraftment was confirmed on day +34. Post-transplant complications included several infectious and inflammatory events. On day +6, the patient developed fever and was diagnosed with *Staphylococcus* bacteremia, and antimicrobial therapy with meropenem and teicoplanin was initiated. On day +10, prednisolone was started for hemophagocytic syndrome (HPS). On day +13, persistently elevated ferritin levels and progressive erythema of the face, extremities, and trunk prompted the initiation of liposomal steroid therapy. Furthermore, elevated total bilirubin levels and transfusion-refractory thrombocytopenia were observed, raising suspicion for sinusoidal obstruction syndrome (SOS). Recombinant thrombomodulin was initiated on day +14. SOS was eventually confirmed based on the lack of clinical improvement and the development of painful abdominal distension, ascites, weight gain, and decreased urine output. Defibrotide therapy was subsequently started. Grade II acute graft-versus-host disease (GVHD) also developed (skin stage 3 and liver stage 1) and was managed with systemic prednisolone. Post-transplant complications were carefully managed along with continuing serial BM evaluations. A stable donor chimerism rate of 99.3% derived from the second donor was maintained through day +100. Given the patient's favorable general condition, he was discharged on day +140. The patient was at 3 years

post-transplantation on the last follow-up. No significant late complications have been observed, and the patient has remained in good condition.

DISCUSSION

Graft failure is a highly devastating complication after UCBT with high transplant-related mortality [9, 10]. Several risk factors have been identified, including insufficient stem cell dose, HLA mismatch, ABO incompatibility, viral infections, inflammatory complications (such as HPS and GVHD), and exposure to broad-spectrum antibiotics [9]. In particular, cell dose is a critical determinant of engraftment after UCBT. Several studies have found a strong association between a CD34-positive cell dose below $1.0 \times 10^5/\text{kg}$ and graft failure or delayed engraftment [7]. Another important determinant of transplantation outcome is HLA compatibility between donor and recipient. Although UCBT tolerates greater HLA mismatch compared with bone marrow or peripheral blood transplantation, increasing HLA disparity is associated with higher risks of graft failure and delayed engraftment [7]. In the present case, the first UCBT involved a low CD34-positive cell dose ($0.73 \times 10^5/\text{kg}$), which was below the widely accepted threshold of $1.0 \times 10^5/\text{kg}$, and significant HLA and ABO mismatch, all of which likely contributed to graft failure. In contrast, the second UCBT utilized a cord blood unit with a substantially higher cell dose and improved HLA compatibility. This difference is consistent with previous observations on cell dose as the most important modifiable risk factor for engraftment failure after UCBT and repeat UCBT [7, 8]. Unfortunately, the cord blood unit that was ultimately used for the second transplantation was not available in the cord blood registry at the time of the initial transplantation and could not be considered during the first donor search.

Furthermore, conditioning regimens for salvage transplantation after graft failure are not standardized. Early reports have promoted so-called “1-day regimens” incorporating cyclophosphamide and low-dose TBI to achieve sufficient immunosuppression [10]. In contrast, single-center and disease-specific reports indicate that fludarabine-based, reduced-intensity regimens combined with alkylators and/or low-dose TBI can provide adequate immunoablation while minimizing regimen-related toxicity, particularly when patients are clinically unstable at the time of salvage [11, 12]. In our patient, reduced-intensity conditioning with fludarabine, cyclophosphamide, and low-dose TBI was followed by infusion of a cord blood unit with substantially higher total nucleated and CD34 cell doses with improved HLA compatibility, resulting in early donor chimerism and durable engraftment.

The feasibility of a second UCBT as a salvage strategy after primary graft failure has been reported in both pediatric and adult populations. Early clinical experiences and small case series have demonstrated that repeat CBT can achieve neutrophil recovery after primary graft failure when units are immediately available and conditioning was appropriate [13]. More recent registry-based analyses have provided stronger evidence of second UCBT as a practical salvage option. In a Eurocord/European Society for Blood and Marrow Transplantation registry analysis of UCBT

performed after graft failure from a prior HSCT, the cumulative incidence of neutrophil engraftment by day 60 was 59.1%, with a median time-to-neutrophil-engraftment of 24 days [10]. Other cohort studies have similarly reported neutrophil recovery after the second UCBT, with median engraftment occurring approximately 3 weeks after transplantation [14].

The choice between a second UCBT and a haploidentical HSCT after graft failure remains controversial. Comparative registry-based studies have shown that although haploidentical transplantation is associated with higher engraftment rates, overall survival appears comparable between haplo-HSCT and second UCBT [10, 15]. However, UCBT is consistently associated with lower rates of severe acute and chronic GVHD than haplo-HSCT, potentially offering an important advantage in pediatric patients with significant comorbidities or active infections [8, 10, 16]. Therefore, second UCBT remains a reasonable and evidence-based salvage option, particularly with the prompt availability of a cord blood unit with an adequate cell dose and acceptable HLA compatibility [15, 17]. The present case further demonstrates the feasibility of repeat UCBT as a salvage strategy, provided that prompt recognition of graft failure and early planning for retransplantation are achieved.

In conclusion, this case illustrates the feasibility of a second UCBT as a salvage option after primary graft failure with early recognition, timely retransplantation, optimized conditioning, and careful graft selection. These findings reinforce the importance of graft cell dose and donor characteristics in ensuring engraftment success and verify the feasibility of a second UCBT as a salvage strategy in selected pediatric patients.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

Our institution does not require ethical approval for reporting individual cases or case series.

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Written informed consent was obtained from the patient or their guardian for their anonymized information to be published in this article.

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