Case Report
Persistent Mixed Donor Chimerism following Double Umbilical Cord Transplantation in a Patient with T-Cell Prolymphocytic Leukemia

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1. Introduction

T-cell prolymphocytic leukemia (T-PLL) is a rare postthymic T-cell neoplasm, accounting for approximately 2% of all leukemia cases, with a greater incidence in males beginning in their sixth decade [1]. Typically, untreated T-PLL is associated with a survival of less than 1 year [2]. The aggressive nature of this disease, and its rarity, presents both diagnostic and therapeutic challenges to physicians [2]. Current standard of care for T-PLL includes the use of alemtuzumab (Campath-1H), a humanized IgG1 antibody specific for the CD52 antigen which is highly expressed on normal and malignant lymphocytes [1, 3]. Thereafter, postremission therapy with either autologous or allogeneic stem cell transplant (SCT) has been associated with disease-free and long-term survival, with a median overall survival of 48 months for both allogeneic and autologous SCT, compared to 20 months for those patients who received alemtuzumab alone [1]. There is a paucity of data on alternative donor transplantation in T-PLL. A Japanese group reported the first case of an umbilical cord blood transplant for T-PLL in 2005 [4]; however, we cannot find subsequent reports of umbilical cord blood transplants for this disease. Accordingly, we report here a second case of umbilical cord transplantation used for T-PLL, employing two umbilical cord units this time. Double umbilical cord blood transplant (dUCBT) is increasingly utilized in adults as it appears to improve outcomes, though almost inevitably only one cord blood unit engrafts, a phenomenon known as single-unit dominance [5]. This case is notable for successful engraftment and complete remission that lasted 16 months despite the presence of residual disease at the time of reduced-intensity transplant. An unusual feature of this case was persistent coengraftment of both umbilical cord units,
2. Case Presentation

A 59-year-old female presented to the local emergency department with reports of fatigue and shortness of breath. The patient was observed to have a WBC >400,000/μL, in addition to pitting edema at the ankles and scattered petechiae. Peripheral smears indicated a marked leukocytosis with atypical blast-like cells. A bone marrow biopsy showed extensive involvement with a T-cell lymphoproliferative disorder with the following immunophenotypes: CD2+, CD4+, CD5+, CD7+, cytoplasmic CD3+, and CD52+, with loss of membrane-associated CD3. Fluorescence in situ hybridization (FISH) indicated a loss of the TCL1 locus, consistent with cytogenetics showing monosomy 14, as well as numerous other abnormalities (complex and monosomalous karyotype), including an addition of 22q. CT imaging indicated splenomegaly and multiple enlarged lymph nodes. Collectively, these findings were diagnostic of T-PLL. This phenomenon of single-unit dominance has been well described [5]. It is thought to be mediated by rejection of one graft by T cells in the dominant graft [10], though predicting which cord will predominate is not possible [7]. Coengraftment and mixed donor/recipient chimeraism have been associated with relapse [6]. Following successful treatment of relapse after dUCBT with alemtuzumab and pentostatin, no recipient chimerism was detectable, while donor 1 engraftment peaked at 95%, but donor 2 still persisted (5%). It is interesting that posttransplant therapy with alemtuzumab and pentostatin brought the patient closer to achieving single-unit dominance, which raises the possibility that anti-T-cell therapy after transplant can promote single-unit dominance and potentially protect against relapse. There is clinical evidence supporting the idea that the presence of specific T-cell populations after transplant can mediate the dominance of one cord blood unit over the other, and preclinical data demonstrating that depletion of immune cell fractions within a graft strongly influences coengraftment [10]. Additional research will be needed to fully elucidate the mechanisms of single-unit dominance after dUCBT and to learn whether immune manipulation in a way that promotes single-unit dominance can reduce relapse risk. This case studies indicated 68% donor 1 and 30% donor 2. A summary of her engraftment analysis is provided in Table 1.

Sixteen months after transplant, she began to experience increased fatigue and developed new leukocytosis. Flow cytometry confirmed a second relapse of the disease. Soon thereafter, retreatment with alemtuzumab and pentostatin began. The patient became profoundly cytopenic following her alemtuzumab and pentostatin therapy. Bone marrow biopsy in mid-October confirmed a third remission, with 99% donor cells, though again with both grafts represented 80% donor 1 and 19% donor 2. She remained in complete remission with incomplete platelet recovery; the percentage of donor 1 increased to 95% and percentage of donor 2 dropped to 5% during this time. Unfortunately, however, after a remission that lasted six months, the patient relapsed for a third time and was refractory to attempts at salvage therapy. She expired after surviving for 29 months following her transplant.

3. Discussion

The phenomenon of single-unit dominance has been well described [5]. It is thought to be mediated by rejection of one graft by T cells in the dominant graft [10], though predicting which cord will predominate is not possible [7]. Coengraftment and mixed donor/recipient chimeraism have been associated with relapse [6]. Following successful treatment of relapse after dUCBT with alemtuzumab and pentostatin, no recipient chimerism was detectable, while donor 1 engraftment peaked at 95%, but donor 2 still persisted (5%). It is interesting that posttransplant therapy with alemtuzumab and pentostatin brought the patient closer to achieving single-unit dominance, which raises the possibility that anti-T-cell therapy after transplant can promote single-unit dominance and potentially protect against relapse. There is clinical evidence supporting the idea that the presence of specific T-cell populations after transplant can mediate the dominance of one cord blood unit over the other, and preclinical data demonstrating that depletion of immune cell fractions within a graft strongly influences coengraftment [10]. Additional research will be needed to fully elucidate the mechanisms of single-unit dominance after dUCBT and to learn whether immune manipulation in a way that promotes single-unit dominance can reduce relapse risk. This case
does illustrate, however, that dUCBT is feasible for T-PLL, and postremission dUCBT should be considered for patients with T-PLL who lack available suitably matched related or unrelated donors. This patient remained relatively responsive to salvage therapies even after relapsing following dUCBT and survived for 12 months following her initial posttransplant relapse and 29 months after transplant. This exceeds the anticipated survival for patients treated with alemtuzumab-based therapies alone without transplant, particularly given detectable residual disease at the time of transplant and treatment with a reduced intensity conditioning regimen.

**Conflicts of Interest**

The authors declare no conflicts of interest regarding the publication of this article.

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