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CASE REPORT

Umbilical cord blood transplantation supplemented with the infusion of mesenchymal stem cell for an adolescent patient with severe aplastic anemia: a case report and review of literature

This article was published in the following Dove Press journal:
Patient Preference and Adherence
11 June 2015
Number of times this article has been viewed

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Abstract: Delayed hematopoietic recovery and increased rate of engraftment failure limit the use of umbilical cord blood transplantation (UCBT). We describe a case of severe aplastic anemia treated by UCBT combined with mesenchymal stem cells. Our case reveals that infusing mesenchymal stem cells early (about 40 days) after UCBT may promote hematopoietic recovery. This experience will guide clinical scientists, especially hematologists, to deal with similar situations and encourage them to widen this strategy.

Keywords: cord blood transplantation, mesenchymal stem cell, aplastic anemia

Introduction

The first successful case of umbilical cord blood transplantation (UCBT) was reported in the 1980s.[1] Nowadays, UCBT is recognized as one of the most significant branches of the hematopoietic stem cell transplantation (HSCT) field. However, the delay of hematopoietic reconstruction and increasing probability of engraftment failure resulting from relatively low counts of hematopoietic stem cells contained in a single cord blood (CB) unit prevent the UCBT from widespread use.[2–4] Many strategies such as double-unit unrelated mismatched UCBT,[4–8] direct bone marrow infusion,[9–11] and ex vivo expansion[12–14] have been studied to overcome the above-mentioned limitations.[15] The first description of mesenchymal stem cells (MSCs) by Friedenstein in 1966[16,17] drew the attention of the biologic field, and the properties of supporting hematopoiesis of MSCs were also shown by Friedenstein in 1974.[18,19] MSCs are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts, chondrocytes, adipocytes, and so on.[20–22] Due to their multilineage differentiation capacity, hematopoiesis-supporting nature, immunomodulation, and secretion of proregenerative factors,[23,24] MSCs have been in the focus of intense research for decades.[21,25] Here we report a case of severe aplastic anemia (SAA) successfully treated by UCBT combined with MSCs.

Case presentation

A 13-year-old Chinese girl who presented with repeated petechia and ecchymoses for 3 days accompanied by nasal bleeding once was admitted to a local hospital. Routine examination of blood revealed that the white blood cell (WBC) count was 2.64×10^9/L, hemoglobin (HGB) was 66.4 g/L, platelet (PLT) count was 9×10^9/L, neutrophil count

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was 0.18×10^9/L, and reticulocyte was 0.3%. Bone marrow examination showed that the bone marrow was extremely hypoplastic, megakaryocytes were absent, non-hematopoietic cells including plasmocyte, fibrocyte, and lymphocyte were increased, fat cells were increased significantly, hematopoietic cells were rare, and the chromosome karyotype was unremarkable; myelodysplastic syndrome (MDS) was not considered. There was no typical hemoglobinuria, Ham test was negative, and paroxysmal nocturnal hemoglobinuria (PNH) was not considered. She was diagnosed as suffering from SAA. After receiving antithymocyte globulin (ATG), cyclosporin, androgen, and component blood transfusion for 8 months, her condition did not improve.

She was then transferred to our hospital. Bone marrow examination showed that the bone marrow was hypoplastic, pancytopenia was noted, megakaryocytes were absent, and the chromosome karyotype was unremarkable. She matched with her sister's umbilical CB (HLA-A, HLA-B, HLA-DR). She was preconditioned with FC regimen (fludarabine 34 mg/m^2, day 1 to day 6; cyclophosphamide 53 mg/kg, day 5 to day 6, with day 1 defined as the first day before UCBT day, and so on). She received 33 mL umbilical CB from her sibling sister with mononuclear cell 9.8×10^6/kg and WBC count 14.1×10^9/L on October 15, 2013. After transplantation, cyclosporin and mycophenolate mofetil were administered to prevent graft-versus-host disease (GVHD), alprostadil to prevent hepatic vein occlusion disease, and acyclovir to prevent cytomegalovirus (CMV) infection. Fluid infusion, alkalization of urine, and mesna were administered to prevent hemorrhagic cystitis. After transplantation, GVHD manifestation such as diarrhea, skin rash, and liver damage did not occur. Intermittent composition blood transfusion was needed. Routine blood examination on day 1 (day 1 is defined as the first day after UCBT day, and so on) showed WBC 0.15×10^9/L, HGB 57 g/L, and PLT 34×10^9/L; other blood analysis results from day 2 to day 41 are shown in Figure 1. Routine blood examination on November 25, 2013 showed WBC 0.62×10^9/L, HGB 62 g/L, and PLT 6×10^9/L. She was still not grafted, and her condition did not improve. She received MSCs (total number 2×10^7, 4.35×10^5/kg, from umbilical cord; Alliancells Bioscience Co., Ltd., People's Republic of China) on November 27, 2013. She had no obvious discomfort during the process or adverse reaction after the process. Routine blood examination before she was discharged showed WBC $3–5\times10^9$/L, HGB 80–90 g/L, and PLT $100–124\times10^9$/L. The shimeric state showed complete donor phenotype. The changing trends of her WBC counts before and after MSC infusion are shown in Figure 1, the HGB counts in Figure 2, and PLT counts in Figure 3. The figures show that after MSC infusion, counts of WBC, HGB, and PLT increased and fluctuated around their normal levels; she was at complete remission and followed up.

Discussion

Compared to bone marrow transplantation (BMT), UCBT provides many advantages. The acquisition of CB is easy, and the collection is harmless both to the mother and the newborn infant. Also, HSCs from the CB graft can be cryopreserved and transplanted to the host after thawing without losing its reproducing ability. Broxmeyer's study found no significant differences of nucleated cells, granulocyte-macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitors after cryopreservation of CB for 10 years.[26] Yamamoto et al reported that the recovery rate of total nucleated cell (TNC) count, CD34$^+$ cell count, and CFU-GM number was not significantly different between the study group (18 CB units, collected between April 1998 and September 1998) and control group (18 CB units, collected between May 2008

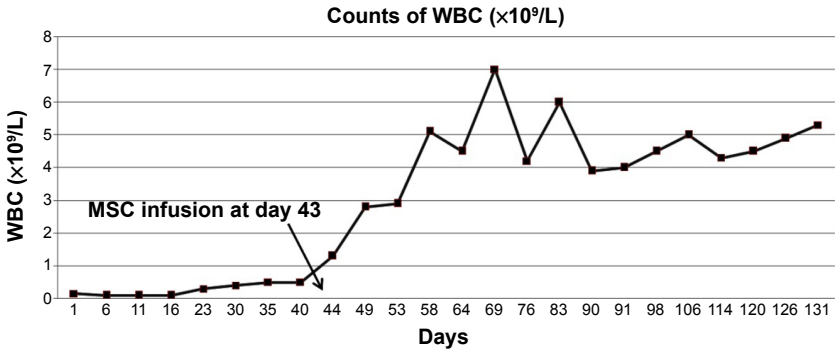

Figure 1 Counts of WBC from day 1 to day 131.
Note: After MSCs infusion, counts of WBC increased and fluctuated around normal level.
Abbreviations: WBC, white blood cell; MSC, mesenchymal stem cell.

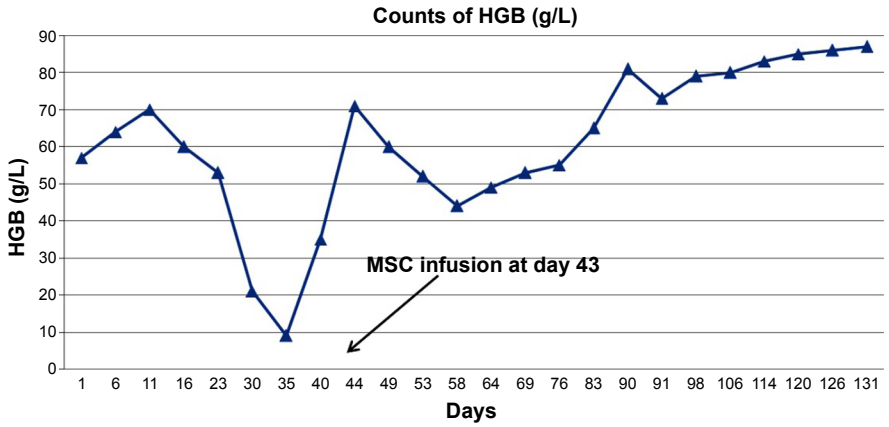

Figure 2 Counts of HGB from day 1 to day 131.
Note: After MSCs infusion, counts of HGB increased and fluctuated near normal level.
Abbreviations: HGB, hemoglobin; MSC, mesenchymal stem cell.

and June 2008).[27] The latest study by Mitchell et al showed that UCB units after cryopreservation for at least 10 years had no impact on the clinical outcome.[28] The incidence of GVHD related to UCBT is generally lower than in BMT. According to Hwang et al GVHD incidence in unrelated UCBT is not higher than unrelated-donor BMT in pediatric patients: chronic GVHD (cGVHD) is lower in UCBT, and acute GVHD (aGVHD) (III–IV) is no different.[29] Zhang et al reported that the incidence rates of both aGVHD and cGVHD were significantly lower in the UBMT group compared with the BMT group in acute leukemia patients.[30] But Chen et al reported that the incidence of Grade 2–4 and 3–4 aGVHD was increased in the UBMT group compared with the BMT group and that the incidence of extensive cGVHD was significantly lower in UCBT.[31] Another obvious advantage of UCBT compared with BMT is the relatively low human leukocyte antigen (HLA)-matching requirements. A high degree of HLA matching is generally required in BMT, namely 6 of 6 (HLA-A, HLA-B, and HLA-DR loci), and only 30% of patients needing allogeneic HSCT can have access to a matched sibling donor.[2] For UCBT, a minimum 4 of 6 HLA allele matching is required, but 5 of 6 is ideal.[32]

While hematopoiesis recovery is slow,[2–4] and infectious complication incidence is high in CB recipients.[33,34] Delayed hematopoietic recovery and increased rate of engraftment failure limit the use of UCBT. Delayed hematopoietic recovery could result in infection complication and increased transplantation-related mortality (TRM). UCBT outcomes have been proven to be closely associated with $CD34^+$ dose or TNC dose.[35] Wagner et al[36] reported that the dose of $CD34^+$ cells was a significant factor related to the rate of engraftment, TRM, and survival in Cox regression analyses. Eapen et al[37] found that with the TNC $>3.0\times10^7$/kg, the overall outcome significantly improved in children with acute leukemia. The $CD34^+$ dose in a CB graft is on average 1–2 log smaller than in an unrelated BM or peripheral blood stem cell graft.[38] Many strategies mentioned in the Introduction are utilized to overcome the low dose limitation in CB.

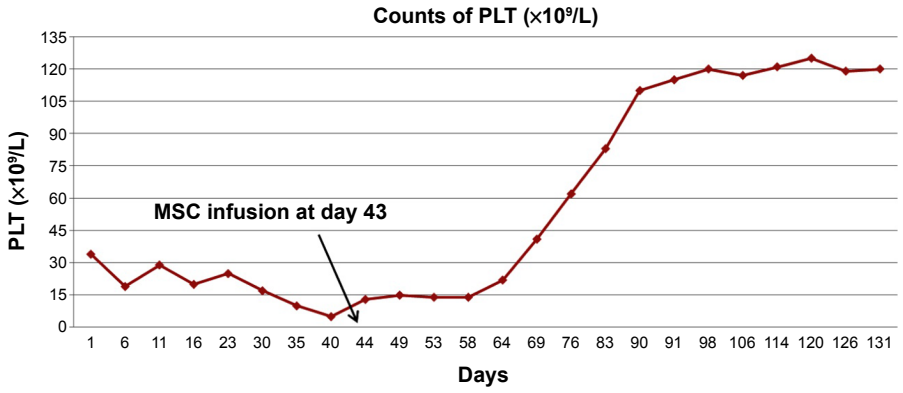

Figure 3 Counts of PLT from day 1 to day 131.
Note: After MSCs infusion, counts of PLT increased and fluctuated around normal level.
Abbreviations: PLT, platelet; MSC, mesenchymal stem cell.

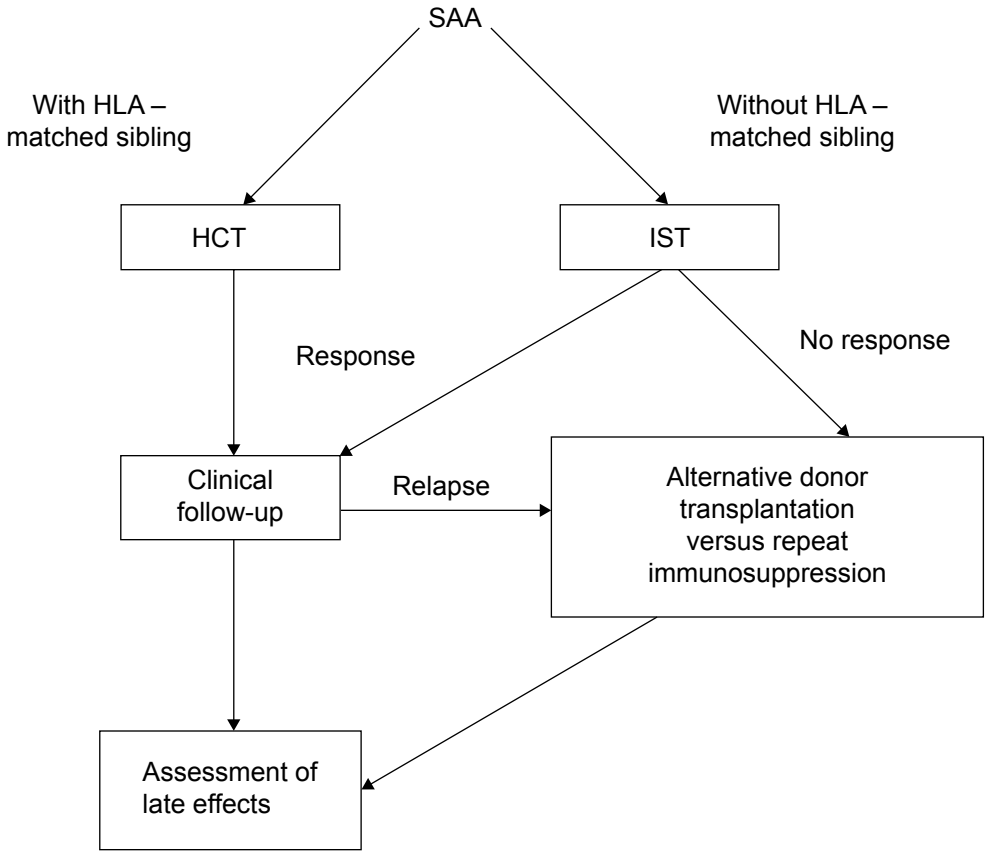

Figure 4 Treatment schema of SAA.
Abbreviations: HLA, human leukocyte antigen; SAA, severe aplastic anemia; IST, immunosuppressive therapy; HCT, hematopoietic cell transplantation.

MSCs can be found in various tissues, such as peripheral blood, umbilical cord and placenta, bone marrow. Because of their properties such as multilineage differentiation capacity, hematopoiesis-supporting nature, immunomodulation, and secretion of proregenerative factors, MSCs have been regarded as potential therapeutic agents in many clinical diseases, in particular for the treatment of hematologic and immunological disorders. MSCs are used to treat autoimmune diseases as well. Constantin et al[39] reported that MSCs derived from adipose administered intravenously before onset of the disease significantly mitigated the severity of autoimmune encephalomyelitis (EAE) due to their immunomodulation properties. As regard to hematological disorders, MSCs are reported to be studied and used in various disorders, maybe due to their properties of hematopoiesis support and immunomodulation. Robinson et al[40] showed that a 10–20-fold increase in TNCs, a 7–18-fold increase in progenitor cells, and a 16–37-fold increase in $CD34^+$ cells could be achieved by coculturing CB cells with MSCs. Nauta et al[41] reported that significant enhancement of long-term engraftment with better tolerance to host and donor antigens was achieved by the addition of host MSCs. The underlying mechanism of the immunomodulation of MSCs is not very clear, but growing evidence reveals that MSCs exhibit immunosuppressive activity on T cells,[42–46] B cells,[47,48] and natural killer (NK) cells.[49–51] The underlying mechanism of hematopoiesis support of MSCs is supposed to be the effect of supporting the reconstruction of hematopoietic microenvironment in addition to direct hematopoiesis.[52–54]

Aplastic anemia (AA) is a disease in which the bone marrow and the blood stem cells are damaged, which causes pancytopenia, including anemia, leukopenia, and thrombocytopenia. Its causes are various, and it is regarded as an autoimmune disorder[55] in which immune cells (mainly T cells)[56] attack the bone marrow and cause pancytopenia. Its first-line treatment consists of hematopoietic cell transplantation and administration of immunosuppressive drugs. SAA is life-threatening and needs immediate treatment. Adolescents and young adults (age <30 years) with SAA who have an HLA-matched sibling donor should proceed directly to hematopoietic cell transplantation;[57–59] the treatment scheme[57] is shown in Figure 4. But this treatment scheme does not consider the situation in which the patients do not respond to hematopoietic cell transplantation.

Table 1 Basic clinical parameters of the other four UCBT patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	12	25	41	41
Sex	Female	Male	Male	Female
Diagnosis	M5	CML	M4	CML
Diagnosis time	9/2003	11/2005	2/2012	9/2002
Main therapeutic schedule	MA and DA	Hydroxyurea	DA	Hydroxyurea
UCBT time, volume, and dose	3/3/2004, 30 mL, missing	11/7/2008, 42 mL, 1.2×10^7/kg	4/26/2012, 5 mL, 2.69×10^7/kg	3/8/2005, N/A, N/A
Interval between UCBT and death	20 days	45 days	85 days	40 days
Whether grafted	Not grafted	Grafted with acute GVHD	Grafted with acute GVHD	Not grafted
Main complication	Central nervous system infection, intracranial hemorrhage	Septic shock, DIC	Respiratory failure, severe pneumonia, acute renal failure	Interstitial pneumonia and acute left heart failure

Abbreviations: M5, acute monocytic leukemia; CML, chronic myelocytic leukemia; M4, acute myelomonocytic leukemia; MA, mitoxantrone + Ara-c; DA, daunorubicin + Ara-c; UCBT, umbilical cord blood transplantation; DIC, disseminated intravascular coagulation; GVHD, graft-versus-host disease; N/A, not applicable.

There have been reports in the literature on the use of MSCs during allogeneic transplantation to enhance engraftment.[60–62] Our patient was an SAA case. She matched with her sister's umbilical CB and was without transplantation-associated contraindications, but she did not respond to immunosuppressive therapy (IST) or UCBT. After failure of the initial UCBT treatment, considering AA is of pancytopenia and an immunity-related disease and the limitation of delayed hematopoietic recovery and increased rate of engraftment failure of UCBT discussed above, we decided to apply MSCs to this patient for its hematopoiesis-supporting properties and immunomodulation. After MSC infusion, the WBC count increased and fluctuated around the normal level; she was on complete remission and followed up.

Before this case, our department had handled four cases of UCBT and they all failed. Their basic clinical parameters are listed in Table 1. The first patient died of central nervous system infection and intracranial hemorrhage. The second one died of septic shock and disseminated intravascular coagulation. The third died of respiratory failure, severe pneumonia, and acute renal failure. The fourth died of interstitial pneumonia and acute left heart failure. Infection was a common cause of death of the four patients after receiving UCBT, and the mean interval between UCBT and death was 47.5 days.

It is still challenging to deal with delayed hematopoietic recovery and to increase the rate of engraftment after UCBT. As discussed above, delayed hematopoietic recovery easily results in infection, and it is hard to control infection if hematopoietic recovery is delayed.

Our case reveals that infusing MSCs early (about 40 days) after UCBT may promote hematopoietic recovery. However, as this is a single case study without a controlled trial, we cannot be sure whether the MSC infusion had any effect in promoting hematopoietic recovery, or whether the initial CB engraftment was just delayed or infusion of MSC with engraftment was just coincidental. Further studies such as controlled trials and more cases are needed to prove the effect of MSC infusion to promote hematopoietic recovery in UCBT. But surely, the hematopoietic-supporting and immunomodulation properties of MSC are increasingly attracting the attention of scientists and clinicians, and our experience will encourage clinical scientists, especially hematologists, to elaborate this strategy while dealing with a similar situation or another.

Acknowledgments

This work was supported by the National Natural Science Foundation of People's Republic of China (Grant no 81170492, 81370673), the National High Technology Research and Development Program 863 of People's Republic of China (Grant no 2012AA022703), the National Key Basic Research Program 973 of People's Republic of China (Grant no 2010CB732404), the Key Medical Projects of Jiangsu Province (Grant no BL2014078), and the Key Discipline of Jiangsu Province (2011–2015).

Disclosure

The authors declare no conflicts of interest in this work.

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