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ORIGINAL RESEARCH

Autoimmune Hemolytic Anemia After Cord Blood Transplantation: A Retrospective Single-Center Experience

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Objective: To describe the incidence, possible risk factors, and treatment options of autoimmune hemolytic anemia (AIHA) occurring after cord blood transplantation (CBT).

Methods: We retrospectively analyzed the patients who underwent CBT at Peking University First Hospital between January 2004 and July 2022.

Results: We totally identified thirty-six patients who received CBT. Median age was 27.5 years (range, 1.6–52). With a median 6 (range 0.6–10.0) years survivor follow-up, six patients developed AIHA (2 Evans syndrome included) at a median of 168 (range, 122–264) days post-CBT for 8% cumulative incidence density 3 years. Its mortality was 50% and mainly associated with concomitant infections (CMV reactivation rate nearly 100%). The possible risk factors for developing AIHA are CMV reactivation, GvHD and HLA mismatch.

Conclusion: AIHA is a clinically significant common complication in recipients post-CBT. Corticosteroids combined with intravenous immunoglobulin (IvIg) is recommended for the treatment of warm antibody AIHA after CBT.

Keywords: autoimmune hemolytic anemia, cord blood transplantation, combination therapy, prognosis

Introduction

Cord blood (CB) is an important stem cell source for patients with hematologic disorders and non-hematologic diseases.[1,2] One of the major complications after allogeneic hematopoietic stem cell transplantation (HSCT) is autoimmune cytopenia (AC), which includes autoimmune neutropenia (AIN), autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), Evans syndrome (AIHA with ITP), and trilineage autoimmune cytopenia (AIN and AIHA with ITP).[3] AIHA is the most common AC after HSCT, but accurate reporting of ITP is challenging because there are many causes of post-transplantation thrombocytopenia.[4,5] These disorders have been recently described among pediatric and adult patients undergoing CB transplantation (CBT), in several case reports or a cohort of patients with malignant and non-malignant diseases.[5–7]

Studies of AIHA occurring after CBT are uncommon and based on case reports or small series, probably associated with graft-versus-host disease (GvHD).[8] These hematologic autoimmune disorders may be related to the use of unrelated donors and development of GvHD, possibly reflecting a dysregulation of the immune system. CB-derived lymphocytes are very naive unlike adult lymphocytes, resulting in decreased stringency of HLA match and lower incidence of GvHD.[8,9] The application of double-unit CBT to overcome the dose limitation of single unit in adults might modify the early immune reconstitution.[10] These genetic and immunologic properties may affect the development of AIHA post-CBT.

This retrospective research was undertaken to characterize incidence, possible risk factors, and treatment options for AIHA developing after CBT in a small cohort of patients in China.

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Patients and Methods

Patients

A total of 36 patients with hematologic disorders and non-hematologic diseases undergoing CBT from unrelated donors or matched related donors at Peking University First Hospital between January 2004 and July 2022 were included in this study. This study was conducted in accordance with the declaration of Helsinki. The institutional review board approved the protocol and written informed consent was obtained from all patients or their guardians. The treatment plans including graft selection, conditioning regimen, immune suppression and supportive care have been reported in detail previously.[11–13]

Conditioning Regimen

The pre-transplantation conditioning regimens varied according to the patient's diagnosis, previous treatment, and disease status. Twenty-two patients were treated with modified busulfan/cyclophosphamide (Bu/CY) regimen. Eleven of them received antithymocyte globulin (ATG) at a total dose of 10 mg/kg. Two patients received a CY/total body irradiation (TBI) regimen. Twelve patients received non-myeloablative regimen. These conditioning protocols were described in detail previously.[11–13]

Prophylaxis and Treatment of GvHD

Twenty-nine patients received the combination of mycophenolate mofetil (MMF), cyclosporine A (CsA), and a short course of methotrexate (MTX) as prophylaxis of GvHD. Only seven patients received CsA and MMF as GvHD prophylaxis.[11–13]

Serologic Tests

ABO group typing and antibody screening tests were performed on donor and recipient samples before transplantation and whenever patients required blood components transfusion. The direct antiglobulin test (DAT) was performed as part of the routine pre-transfusion compatibility testing. If positive, further testing with specific anti-IgG and anti-C3d reagents was carried out.

Definitions

AIHA was diagnosed in patients fulfilling all of the following criteria: positive DAT, positive indirect antiglobulin test with broad reactivity to RBC in serum and eluate, clinical and laboratory evidence of hemolysis (increased lactate dehydrogenase and bilirubin levels, decreased Hb and haptoglobin levels and increased transfusion requirements) and exclusion of other causes of hemolysis.[14] ITP was a diagnosis of exclusion, defined as isolated thrombocytopenia in the absence of other causes that may be associated with a low platelet count.[15] The response to therapy was assessed according to previous criteria.[14,16]

Hematopoietic Recovery and Engraftment

Hematopoietic recovery was defined as time to ANC $\geq 0.5\times10^9$/L (first of the 3 consecutive days) and platelet count $\geq 20\times10^9$/L (first of the 7 days without transfusion).

Hematopoiesis by donor cells was ascertained by testing for cells with the donor's ABO type, HLA antigen, sex chromosome, or a combination, in the recipient's PB or BM. Donor chimerism was determined serially on BM and/or PB at days 30, 60, 100, 180, and 360 after transplantation, with additional time points as needed.

Results

Patient and Graft Characteristics

Thirty-six patients with leukemia, malignant lymphoma, aplastic anemia, metachromatic leukodystrophy (MLD), pyruvate kinase deficiency (PKD) and inflammatory bowel disease (IBD) underwent CBT. Patients and graft characteristics are summarized in Table 1. Twenty-eight patients received double-unit CBT, while eight patients received single-unit

Table 1 Patients and Graft Characteristics

Characteristics	Median(Range)	N(%)[#]
Male gender		16(44.4)
Diagnosis		
AML		21(58.3)
ALL		5(13.9)
CML		3(8.3)
AA		2(5.6)
HL		1(2.8)
IBD		2(5.6)
PKD		1(2.8)
MLD		1(2.8)
HLA compatibility		
6/6, 6/6		1(2.8)
6/6, 5/6		1(2.8)
5/6, 5/6		2(5.6)
5/6, 4/6		7(19.4)
4/6, 4/6		17(47.2)
6/6		1(2.8)
5/6		5(13.9)
4/6		2(5.6)
ABO mismatch		
No		7(19.4)
Minor		19(52.8)
Major		7(19.4)
Bidirectional		3(8.3)
Donor-recipient gender mismatch		
No		8(22.2)
One		23(63.9)
Both		5(13.9)
Total nucleated cells infused × 10^7/*kg*	7.9(3.1–25.4)	
Total CD34$^+$ *cells infused* × 10^5/*kg*	3.2(0.7–11.7)	

Note: [#]Because of rounding percentages may not add 100%.
Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; AA, aplastic anemia; HL, Hodgkin lymphoma; IBD, inflammatory bowel disease; PKD, pyruvate kinase deficiency; MLD, metachromatic leukodystrophy; HLA, human leukocyte antigen; GvHD, graft-versus-host disease.

CBT. Median age was 27.5 years (range, 1.6–52). Majority of patients had a baseline diagnosis of acute myeloid leukemia (58.3%). Median number of total nucleated cells and $CD34^+$ cells infused was 7.9×10^7/kg (range, 3.1–25.4) and 3.2×10^5/kg (range, 0.7–11.7), respectively. Most patients (80.6%) received a donor-recipient gender mismatched graft. All patients had a negative DAT at time of transplantation.

Hematopoietic Recovery

Fifteen patients died at the end of follow-up (3/6 of the patients with AIHA, while 12/30 of the other patients). Ten patients failed to hematopoietic recovery after CBT. The other twenty-six evaluable patients had neutrophil engraftment at a median of 19 (range, 11–34) days, and platelet engraftment at a median of 36 (range, 16–209) days.

AIHA and Evans Syndrome

Incidence and Characteristics of AIHA and Evans Syndrome

AIHA was diagnosed in six patients who fulfilled the definition criteria, two of which with concomitant ITP were diagnosed Evans syndrome. Median time from transplant to AIHA or Evans syndrome was 168 (range, 122–264) days. At the onset of AIHA, median values of laboratory parameters were: Hb 5.1 g/dL (normal range, 2.8–9.2), reticulocyte count 161.5×10^9/L (normal range, 17.1–451.4), lactate dehydrogenase 482 U/L (normal range, 263–707), and indirect bilirubin 0.4 mg/dL (normal range, 0.1–0.6). Five patients required transfusion support. One of them died of acute severe hemolysis quickly and the other four received a median of 8 packs (2–19) RBCs. One patient received 3 packs platelets.

Characteristics of patients that developed AIHA or Evans syndrome are shown in Table 2. Five patients were in complete remission (CR) and had complete donor chimerism at time of diagnosis, while the other one relapsed. Three patients with early AIHA had acute GvHD (grade II in two patient and grade IV in the other one). Only one of these patients had chronic GvHD. Concomitant infection at the time of AIHA were present in all patients. Six patients had a cytomegalovirus (CMV) reactivation, including three cases of pulmonary polymicrobial infection (Pseudomonas aeruginosa, Klebsiella pneumoniae) and probable invasive fungal disease (IFD). One patient had pulmonary tuberculosis.

Serological Data

Major and bidirectional ABO mismatch between donor and recipient was present in five patients, whereas minor mismatch was present in one patient. All of the six patients in this study developed AIHA caused by warm antibodies (IgG/C3d). Three out of four patients had concomitant antinuclear antibody (ANA) and platelet associated immunoglobulin (PAIg), while one patient had multiple anti-rheumatoid (Rh) antibodies (including ANA, anti-nucleosome antibody, and anti-histone antibody). No antibodies against the ABO system were found in these patients.

Treatment and Outcome

All patients with AIHA and Evans syndrome were treated except for one patient who subsequently relapsed and died of acute severe hemolysis in two days. Intravenous immunoglobulin (IvIg, 0.4 g/kg/day for 5 days) was the first treatment administered in the remaining three patients. At the same time, prednisone or methylprednisolone (at doses ranging from 1–2 mg/kg/day) were administered. Only three of them achieved partial remission (PR), and the AIHA did not relapse at the end of follow-up.

Discussion

AIHA is a relatively common complication and may occur after any type of allogeneic HSCT, especially after CBT. Few cases on AIHA after CBT have been reported in China. The present research indicated its incidence was high to 16.7%.

Table 2 Characteristics of Patients with AIHA and Evans Syndrome

Patient	Age (Years)	Baseline Diagnosis	ABO Mismatch	Antibody Specificity	Time to AIHA/ES (Days)	Concomitant GvHD	Concomitant Infections	Outcome
1	20	AML	Major	ANA, PAIg	264	No	CMV, Probable IFD, Pseudomonas aeruginosa	Death
2	22	AML	Major	PAIg	169	Acute	CMV, Tuberculosis	Alive
3	31	AML	Bidirectional	ANA, PAIg	135	Chronic	CMV	Alive
4	39	AML	Minor	ANA, Anti-Rh	122	Acute	CMV, Probable IFD, Klebsiella pneumoniae	Death
5	11	AML	Major	No	150	Acute	CMV	Death
6	2.7	PKD	Major	No	180	No	CMV, Probable IFD	Alive

Abbreviations: ANA, antinuclear antibody; PAIg, platelet associated immunoglobulin; CMV, cytomegalovirus; Rh, rheumatoid.

Meanwhile, the 3-year cumulative incidence density was 7.1%. AIHA after CBT occurred in approximately 5% of patients according to previous reports.[7,8] The reasons for higher incidence may be as follows. Our study included 25% of pediatric patients, predominantly HLA mismatch donors, with a CMV reactivation rate up to 70%. González-Vicent et al found that patients less than 15-year-old, and patients using CB or an HLA mismatch donor were more likely to develop AIHA.[17] The development of AC was strongly associated with the presence of chronic GvHD.[8] The chronic GvHD was more frequently extensive after CBT, which led to the higher incidence. Our research mainly focused on adults that were transplanted for hematologic malignant diseases. In this regard, a retrospective single-center study may more reliably reflect the true incidence of the complications in China.

AIHA is also closely related to the presence of various infections. Concomitant infections were frequently observed at the time of diagnosis of AIHA. The CMV reactivation seems to be extremely common in this study. An intriguing possibility is that some of these infections could have triggered an abnormal immune response. In this aspect, the danger model of autoimmunity suggests that signals of damaged cells after exposure to infectious agents can bind to antigen-presenting cells (APCs) and activate a systemic immune response.

Most of patients with AIHA were ABO-mismatch between donor and recipient, which indicated blood group incompatibility was associated with hemolysis. Regarding serological data, all patients had IgG mediated warm antibodies directed against antigens of the rhesus system. This is similar with what was previously reported.[18,19] No association between AIHA diagnosis and whether autoantibodies positive was noticed.

AIHA is a complication of allogeneic HSCT associated with poor prognosis. However, an optimal therapeutic approach is lacking. This study included a small group of pediatrics and adults with hematological and non-hematological disorders that received CBT at a single institution using a relatively homogeneous conditioning strategy, GvHD prophylaxis and supportive care, as well as monitoring for autoimmune complications. Response to therapy was disappointing and overall mortality was high. One patient died of concomitant infection, massive uncontrolled hemolysis was the cause of death in two patients who did not respond to first-line of treatment. Despite aggressive therapy, a similar clinical behavior was recently reported.[20] Earlier identification and diagnosis of AIHA is key to improving efficacy and survival. In cases of sudden drop in Hb or an increase in transfusion requirements, early diagnosis of AIHA should be considered. All cases of warm antibodies AIHA may impact the choice of therapy. In particular, it is advisable to define the best choice, sequence and combination of drugs during different phases of disease. Corticosteroids combined with IvIg are preferred for early treatment. Our findings could help to increase awareness toward AIHA after CBT and guide therapy in these autoimmune complications. Most patients with AIHA failed to respond to corticosteroids or IvIg and needed further treatment. Rituximab and sirolimus are effective options, especially for patients with cold agglutinin disease.[21]

In conclusion, AIHA is a clinically significant common complication in recipients post-CBT. CMV reactivation, GvHD and HLA mismatch seem to increase the risk of developing AIHA. Earlier identification and diagnosis of AIHA is critical to improving efficacy and survival. Its prognosis was poor and mainly associated with concomitant infections. Corticosteroids combined with IvIg is recommended for the treatment of warm antibody AIHA after CBT. If ineffective, adjustment of immunosuppressant therapy should be initiated early.

Disclosure

The authors report no conflicts of interest in this work.

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