

## Original Article

# SAA patients encountering multiple organ failure and severe infections during pretreatment was rescued with haplo-HSCT and unrelated BMSC infusion and achieved transplantation success: a case report and literature review

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**Abstract:** Objective: This study aims to investigate the treatment strategy of haploidentical hematopoietic stem cell transplantation (haplo-HSCT) for patients with severe aplastic anemia (SAA) combined with severe complications. Methods: A patient with SAA was treated with haplo-HSCT combined with unrelated bone marrow-derived mesenchymal stem cell (BMSC) infusion. During the pre-treatment, the patient encountered multiple organ failures and severe infections, but was successfully rescued; and the transplantation was also successful. The data of this patient were analyzed and related literatures were reviewed. Result: A 31-year-old male patient with SAA was treated with haplo-HSCT combined with unrelated BMSC infusion. During pretreatment, the patient encountered sepsis, acute cardiac insufficiency, pulmonary infection, respiratory failure, peritonitis and renal insufficiency, but was successfully rescued; and the transplantation was successful. Conclusion: Haplo-HSCT combined with unrelated BMSC infusion has significant curative effect on SAA. When serious complications occur during the transplant process, patients should not be given up.

**Keywords:** Severe aplastic anemia (SAA), haplo-HSCT, mesenchymal stem cell (BMSC), multi-system infection, multiple organ failure

## Introduction

Severe aplastic anemia (SAA) is a kind of bone marrow failure diseases that seriously endangers the life of patients. Furthermore, general treatment methods for SAA have poor curative effects and high mortality. At present, the main methods for SAA treatment include allogeneic hematopoietic stem cell transplantation (allo-HSCT) and immunosuppressive therapy (IST) [1-3]. Antithymocyte globulin (ATG), cyclosporine (CsA) and other ISTs are effective methods for the treatment of SAA. However, the patient's hemogram requires 3-6 months to restore to normal levels after ATG and CsA therapies, infections and bleeding often occur during this period, and the infections are often difficult to control; which result in high mortality. In addition,

clonal abnormalities are prone to occur in the late stage; hence, the five-year event-free survival rate is only 35-50% [4-6]. Compared with IST, allo-HSCT can decrease its recurrence and clonal changes, and the curative effect is better. Thus, it has become one of the important means of curing SAA [7, 8]. In 2006, the American Hematology Annual Meeting has recommended sibling HLA-identical hematopoietic stem cell transplantation as the preferred treatment method for SAA patients aged less than 40 years old. However, in China, few patients can find HLA-identical donors due to the special national condition, while in young patients this ratio is even lower. In addition, searching unrelated HLA-matched donor requires approximately half a year, which is not suitable for SAA patients who need immediate transplantation.

## SAA rescued with haplo-HSCT and third-party BMSC infusion

Therefore, it is very necessary to explore the treatment of SAA with haploidentical hematopoietic stem cell transplantation (haplo-HSCT). In this study, the authors report the treatment process of one SAA patient, who was treated with haplo-HSCT combined with unrelated bone marrow mesenchymal stem cell (BMSC) infusion. During pretreatment, the patient encountered sepsis, acute cardiac insufficiency, pulmonary infection, respiratory failure, peritonitis and renal insufficiency, but was successfully rescued and the transplantation was also successful. The data of this patient was analyzed and related literatures were reviewed.

### Materials and methods

#### *Conditions introduction*

*History of present illness:* The patient is a 31-year-old man, who is a resident in Zhongshan City, Guangdong Province. He was admitted on December 14, 2015 due to “skin bleeding points for one month”. The patient developed bleeding points in the skin without apparent inducement a month ago, had no fever and no fear of cold, and soon developed a few gingival bleedings. Hence, the patient received dental treatment at the oral branch of Zhongshan People’s Hospital. During the course of the disease, the patient had mild fatigue; but had no obvious dizziness and heart palpitations. Routine blood tests in the branch of traditional Chinese medicine revealed that: white blood cell (WBC) count was  $1.57 \times 10^9/L$ , hemoglobin (Hb) was 71 g/L, and platelet (PLT) count was  $5 \times 10^9/L$ . The patient was admitted for further diagnosis and treatment. Since its onset, the patient had poor spirit, appetite and sleep, and basically normal defecation. However, his body weight change was unknown.

*Past history:* The patient had a history of gout, no history of hepatitis, tuberculosis and other infectious diseases, no history of food and drug allergy, no history of trauma surgery, and no history of blood transfusion.

*Personal history:* The patient had no history of infected water contact, no smoking, drinking and other bad hobbies, and denied visiting prostitutes. In addition, family history did not reveal any special disease.

#### *Admission examinations*

T: 36.5°C; P: 110 times/min; R: 20 times/min; BP: 117/60 mmHg. Patient had a lucid mental

status. Bleeding points were scattered throughout the whole body, and were more obvious in the lower limbs. Superficial lymph node enlargement could not be felt. No tenderness was found in the chest. Cardiac and pulmonary abnormalities were not detected. The liver and spleen could not be palpated.

#### *Adjuvant examinations*

Routine blood tests: WBC,  $1.95 \times 10^9/L$ ; Hb, 64 g/L; PLT,  $2 \times 10^9/L$ ; Ret,  $25 \times 10^9/L$ . The detection of T cell subsets revealed a decrease in CD4/CD8 ratio (0.93); serum uric acid: 507  $\mu\text{mol/L}$ ; serum creatinine: 106  $\mu\text{mol/L}$ . Liver functions: ALT, 26 U/L; AST, 19 U/L; TP, 60.7 g/L; ALB, 39.5 g/L; TBIL, 20.6 g/L, DBIL, 6.4  $\mu\text{mol/L}$ ; IBIL, 14.2  $\mu\text{mol/L}$ . Four items of iron deficiency: serum iron, 39  $\mu\text{mol/L}$ ; serum ferritin, 784 ng/ml; serum transferrin, 1.6 g/L; total iron binding capacity, 47  $\mu\text{mol/L}$ ; serum EPO, >750 mIU/ml. No abnormalities were found in the first eight items of blood transfusion. Blood folate and VitB12 concentration were normal. Ferritin was 784 ng/ml. The eight items of immunity, 12 items of autoantibodies, and thyroid function were all normal. EBV-DNA and CMV-DNA were negative. Tumor markers were negative.

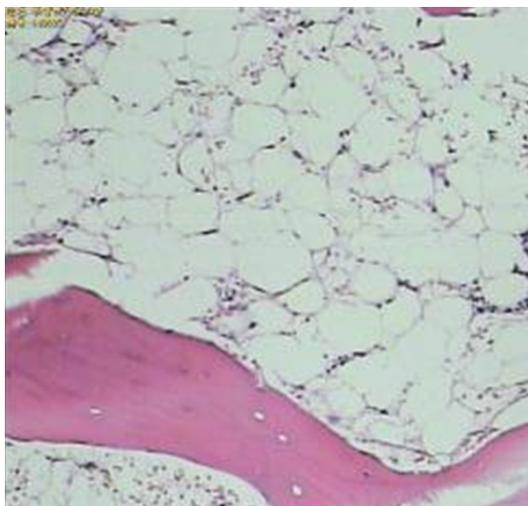
On December 14, 2015, routine test results of the posterior superior iliac spine bone marrow were as follows: karyoplasma development imbalance was detected in bone marrow erythroblasts, megalokaryocytes were not found, and PLT count was reduced.

On December 14, 2015, bone marrow biopsy results were as follows: bone marrow proliferation was extremely low, the medullary cavity was almost filled with adipocytes, only a small amount of myelocyte and metamyelocyte were scattered in the cavity, and no megalokaryocyte was found (**Figure 1**). Silver staining result was negative (-).

On December 14, 2015, MDS-FISH detection results were as follows: All indexes of the sample were less than the positive reference value.

On December 14, 2015, bone marrow molecular karyotyping results were as follows: No abnormality was found.

On December 14, 2015, bone marrow detection results by flow cytometry were as follows: Significant evidence of immune phenotypes



**Figure 1.** Bone marrow proliferation was extremely low, the medullary cavity was almost filled with adipocytes, only a small amount of myelocyte and metamyelocyte were scattered in the cavity, and no megakaryocyte was found.

associated with acute leukemia, NHL and high risk MDS were not detected, while the PNH clone was not detected. CD34<sup>+</sup> cells accounted for 0.3% of the total number of karyocytes.

On December 24, 2015, routine tests results of the bone marrow were as follows: granulocytes and erythrocytes proliferated and karyoplasma development imbalance was found; the density of megakaryocytes was 2 cells/slide; PLT count was reduced; the bone marrow parvule was rich in fibrous skeletons, in which the contained cells were mainly non-hematopoietic cells.

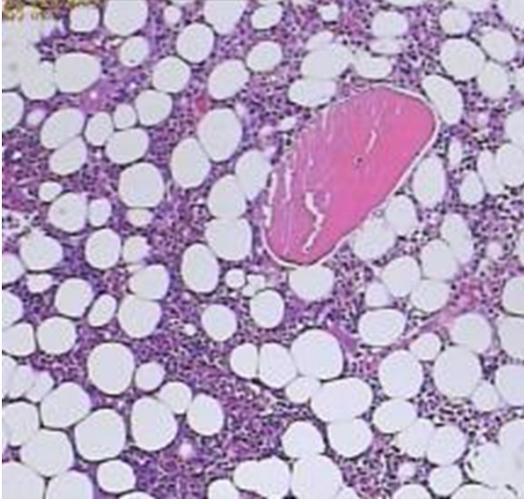
On December 24, 2015, analysis results by flow cytometry were as follows: Approximately 31% of cells were naive B cells, and the immune phenotype did not exhibit obvious abnormalities. Naive B cells were suspected to derive from B progenitor cells. If the possibility of tumor cells could not be excluded in the clinical tests, IgH gene rearrangement should be additionally conducted. Subsequently, IgH and IgK gene rearrangements were conducted, and monoclonal rearrangement was not detected. Marrow CD34<sup>+</sup> cells accounted for 0.25%.

### *Diagnosis and treatment course*

After admission, the patient's hemogram was repeatedly reviewed; and it was found that the whole blood cells were severely reduced. The

HLA match between the patient and his elder sister was HLA5/10 (haploidentical). The diagnosis drawn in the consultation consisted of experts in the department that the author work for was SAA (type I). The patient and his family signed the consent to undergo a haplo-HSCT. The proposed transplantation protocol was as follows: Pretreatment protocol: BU: 3.2 mg/kg/d, *i.v.*, at day -7 and day -6; CTX: 50 mg/kg/d, *i.v.*, from day -5 to day -2; Graft-versus-host disease (GVHD) prevention protocol: CsA + MTX + MMF. Among these, CsA: the dose was 2.5-3.0 mg/kg/d, first intravenous injection, followed by an oral use, from day +180 the dose was gradually reduced; MTX: 15 mg/m<sup>2</sup> at day +1, and 10 mg/m<sup>2</sup> at day +3, +6 and +11. MMF: 0.5 g, *p.o.*, at hour 1/12, and from day -9 to day +30; while 0.25 g, *p.o.*, from day +30 to day +60. Unrelated mesenchymal stem cell (MSC) infusion was performed at day 0 and within six hours before transfusion. Then, this was performed at day +14 again.

On January 11, 2016, the patient was transferred into the laminar flow room. On January 12, 2016, pretreatment was initiated. On January 13, 2016, serum creatinine level increased to 199  $\mu$ mol/L, CsA treatment was temporarily suspended, and FK-506 *i.v.* drips were used instead. On January 15, 2016, the patient began to have hyperpyrexia, and had a body temperature of 39.9°C, which was combined with fear of cold and lack of strength. Furthermore, the patient had mild nausea; and encountered diarrhea several times at an amount of approximately 500 ml. Blood culture revealed a positive result of Gram-negative bacteria (*Escherichia coli*). Imipenem and linezolid were given for anti-infection, and posaconazole was given for anti-fungus. On January 18, 2016, the patient had persistent fever, tachypnea, orthopnea and cyanosis of the lips. Bubbles could be heard in both lungs. Blood gas analysis revealed 49 mmHg of partial pressure of oxygen (PO<sub>2</sub>), 28 mmHg of partial pressure of CO<sub>2</sub> (PCO<sub>2</sub>), and 68% of blood oxygen saturation. Blood BNP was significantly elevated (up to 10,213 pg/ml). Whole abdominal muscles were tense, and had tenderness and rebound tenderness. Both lower limbs had subsidence edema. The patient was considered to have pulmonary infection, as well as type I respiratory failure, acute cardiac insufficiency, peritonitis and sepsis. The amount of liquid intake was immediately controlled. Cardiotonic drugs,



**Figure 2.** Microscopic examination of the bone marrow revealed a generally normal proliferation, and adipose cells accounted for 50% of the medullary cavity volume. The granulocytes/erythroblasts ratio was roughly normal, these cells were mainly myelocytes and metamyelocytes, respectively. A considerable number of megakaryocytes were found, and no significant morphological abnormalities were found.

diuretic drugs, oxygen supply by high flow mask and other measures were administered. The original antibiotics were discontinued, and tigecycline + sulperazone + mycamine were used for anti-infection instead. Glucocorticoid (budesonide) was nebulized and inhaled. At 9 o'clock in the morning, January 19, 2016, patient was transferred to the ICU in the Internal Medicine Department and received noninvasive mechanical ventilation. At 12 o'clock of the same day, MSCs were infused; and at 2 o'clock in the afternoon of the same day, bone marrow from the donor was infused. At 2 o'clock in the afternoon of the next day (January 20, 2016) peripheral blood stem cells from donor were infused (total amount in bone marrow + peripheral blood:  $3.87 \times 10^6$ /kg of CD34<sup>+</sup> cells, and  $8.45 \times 10^6$ /kg of mononuclear cells). At the same time, anti-infection, high flow oxygen, cardio-tonic drugs and diuretic drugs were continued. On January 23, 2016, the patient's body temperature returned to normal, heart failure was controlled, and PO<sub>2</sub> and saturation levels returned to normal. After the condition became stable, the patient was transferred to the laminar flow ward. The patient continued to receive MTX, MMF and FK-506 treatments for a short period to prevent GVHD and promote hematopoiesis. At 14 days after transplantation, exam-

inations revealed the following results: WBC count was  $1.55 \times 10^9$ /L, NE was  $1.11 \times 10^9$ /L, Hb was 87 g/L, and PLT count was  $19 \times 10^9$ /L. This indicated hematopoietic reconstitution. CMV-DNA was positive. Ganciclovir and immunoglobulin anti-CMV therapy was administered. On February 2, 2016, the patient's serum creatinine returned to normal (94  $\mu$ mol/L). On February 2, 2016, the patient developed hematuria, urinary frequency and odynuria. It was suspected that the patient had developed hemorrhagic cystitis; hence, symptomatic supportive therapy was administered. On March 3, 2016, urinary frequency, odynuria and other symptoms disappeared; and urine color turned to transparent.

#### *Final diagnosis*

(1) SAA (type I), (2) post allo-HSCT status (5/10 HLA-identical, elder sister for younger brother, O+ for O+), (3) sepsis, (4) acute cardiac insufficiency, (5) pulmonary infections and respiratory failure, (6) gout and renal insufficiency, (7) acute peritonitis, (8) cytomegalovirus infection, and (9) hemorrhagic cystitis.

#### **Results**

At 14 days after transplantation, white blood cells were activated. At 27 days, PLTs survived. At 42 days after transplantation, red blood cell transfusion was discontinued, hemogram became stable, no infection, bleeding and anemia was found. On April 28, 2016, recheck of the bone marrow revealed that: karyocytes actively proliferated. The chimeric rate of the bone marrow transplantation donor cell DNA was 100%. On May 6, 2016, routine blood test results were as follows: WBC count was  $2.96 \times 10^9$ /L, Hb was 96 g/L, and PLT count was  $50 \times 10^9$ /L. On July 17, 2016, routine blood test results were as follows: WBC count was  $8.44 \times 10^9$ /L, Hb was 95 g/L, and PLT count was  $95 \times 10^9$ /L. Bone marrow cytology: The bone marrow granulocyte, erythrocyte and megakaryocyte three series proliferated after treatment for aplastic anemia (AA). Bone marrow biopsy: Microscopic examination of the bone marrow revealed a generally normal proliferation, and adipose cells accounted for 50% of the medullary cavity volume. The granulocytes/erythroblasts ratio was roughly normal, these cells were mainly myelocytes and metamyelocytes, respectively. A considerable number of mega-

karyocytes were found, and no significant morphological abnormalities were found (**Figure 2**). The chimeric rate of the bone marrow transplantation donor cell DNA was 100%.

### Discussion

For young patients with SAA who have no response to immunosuppressive therapy, if unrelated HLA-identical donors could not be found, how do they decide? Previous studies reported that some research centers have attempted to study on haplo-HSCT treatment for SAA patients. From the 1980s to the mid 1990s, studies [9, 10] have suggested that the failure rate of haplo-HSCT without an identical donor and the incidence of GVHD was high. Hereafter, with the improvement of the transplantation regimen [11], the effective rate of haplo-HSCT in the SAA patient has been improved. Deeg *et al.* [12] believed that unmatched HLA is the most important factor that affects the survival of patients.

In 2009, Fang B *et al.* [13] reported two refractory SAA child patients who had failure of implantation and underwent MSC + haplo-HSCT infusion. During the two years of followed-up, patients did not need any treatment and blood transfusion; and their conditions were good. Therefore, they believed that the concurrent transplantation treatment of haplo-HSCT with MSC may promote the hematopoietic implantation in patients with implantation failure. Wang H *et al.* [14] also reported the treatment of a SAA puerile patient who had no response to steroid, cyclosporine and filgrastim treatments. The patient was treated with haplo-HSCT from her father, and BMSCs were infused at a dose of  $1.25 \times 10^6/\text{kg}$ . The hematopoietic implantation in this patient was rapid, and acute/chronic GVHD was not detected, hence the patient achieved a good living condition. Thus, they also believed that the co-infusion of haplo-HSCT with MSC should be attempted in SAA patients without HLA-identical donors. Jaganathan *et al.* [15] reported the treatment of a 26-year-old SAA patient, who was treated with unrelated identical allo-HSCT after the failures of two courses of ATG treatment. A total of four HSCT treatments were conducted on this patient. The first three implantations all failed; and for the last time, a dose of  $1 \times 10^6/\text{kg}$  of MSC deriving from a unrelated

donor were infused, finally achieving hematopoietic implantation. The same dose of MSC from the same donor was re-transfused at 26 days after transplantation. Excitingly, the hematopoiesis of the patient completely recovered. Bone marrow biopsy revealed that there was almost no hematopoietic tissue in the bone marrow of patients before transplantation, while another bone marrow biopsy at 25 days after the last transplantation revealed the recovery of the hematopoietic system. In addition, Fang B *et al.* [16] reported that two patients developed secondary refractory pure red cell aplasia (PRCA) after ABO-incompatible HSCT infusion, and received MCS vein injection at a dose of  $1.5 \times 10^6/\text{kg}$ , after the failure of traditional treatment. As a result, the patient's hematopoietic function quickly recovered, and no side effect occurred. Therefore, they put forwarded that MSC has a good application prospect in patients with PRCA secondary to failure of ABO-incompatible HSCT.

At present, there are some problems in SAA transplantation, such as rare sibling donors and poor curative effect of ATG. Unrelated-donor transplantation has expanded the selection range of the transplantation donor, while it also brings about some problems such as failure of implantation and high incidence of GVHD. Both theories and the results of the present clinical studies on MSC suggest that MSCs combined with HSCT can promote hematopoietic implantation with unrelated donors, and in which GVHD can be prevented or treated. At present, at home and abroad, some cases or small sample studies have reported that MSCs combined with unrelated donor transplantation have obtained good clinical results. Preliminary studies conducted by Zenghui Liu *et al.* confirmed that BMSC infusion could upregulate the proportion of  $\text{CD4}^+\text{CD25}^+\text{FoxP3}^+$  Treg in peripheral blood in patients with AA [17], Xiao Y *et al.* reported that the response rate of BMSC treatment in refractory AA patients who achieved poor curative effect in IST was high in earlier stage, and had few side effects and high safety [18]. Other studies also revealed that, bone marrow combined with peripheral blood stem cell transplantation could promote its implantation and reduce the incidence of GVHD [19, 20]. MSCs have immune suppression function and immune incompetence, and can support the function of hematopoiesis and immune regula-

tion [21, 22]. All of these suggest that MSCs combined with HSCT has a good clinical application prospects in SAA patients.

In the patient in this study, the hemogram severely decreased and proliferation of the bone marrow was extremely low, the conditions were critical. There was no sibling HLA-identical donor, but a sibling HLA-haploidentical donor. The department in which the author work has joined the multi-center research project of Guangdong province, a clinical study on selective donor transplantation combined with unrelated BMSC infusion in SAA patients. Pre-treatment protocol: BU: 3.2 mg/kg/d, *i.v.*, at day -7 and day -6; CTX: 50 mg/kg/d, *i.v.*, from day -5 to day -2. During pre-treatment, the patient developed acute renal dysfunction and *Escherichia coli* sepsis. According to drug sensitivity, imipenem and linezolid were used for anti-infection, and posaconazole was used for anti-fungus. However, pulmonary infections combined with respiratory failure type I and peritonitis successively occurred. Acute cardiac insufficiency occurred at the day of transplantation (BMSCs), the conditions of the patient was critical, and there is immediate danger in the patient's life. After discussion and expert consultation in the department, although having very low hemogram, the patient was transferred to the ICU in the Internal Medicine Department and received noninvasive respiration for life support. At the same time, cardio-tonic drugs and diuretic drugs were administered, in order to improve heart function, reduce pulmonary congestion and edema, and actively prevent infections (bacteria and fungi). The patient underwent transplantation according to the plan. Breathing difficulty was significantly improved two days after transplantation. The review of blood gas revealed 90 mmHg of PO<sub>2</sub> and normal PCO<sub>2</sub>. Pulmonary bubble significantly reduced, the ventilator was disconnected, and fever faded away at four days after transplantation. Hence, patient was transferred to the laminar flow ward. Acute renal insufficiency occurred during the transplantation, and serious infections (sepsis and pulmonary infections combined with type I respiratory failure), acute left heart failure and other life-threatening complications occurred during the aplastic stage. The patient turned the corner after effective treatments (such as respiratory support, heart function improvement, timely replacement of anti-infection treatment, blood transfu-

sion and other supportive treatments), which ensured the smooth process of the transplantation, fighting for the opportunity to the cure of the disease. The mortality rate in general patients with these serious complications was 40-50% [23, 24]. The patient was diagnosed with SAA, whose hemogram revealed a severe decrease and the patient's peripheral blood had almost no neutrophil after pretreatment. Under this condition, mortality rate was as high as 90% or more if severe multiple infections occur [25, 26]. Anti-infection treatments should not only rely on drug sensitivity tests, but also depend on its clinical effect. The treatment proposed according to drug sensitivity tests had a poor curative effect when the sepsis occurred in this case, thereby antibiotics were decisively replaced (tigecycline was not used in the drug sensitivity test), and further respiratory support from the ICU was timely sought for. Since the patient had cardiac insufficiency, if cardiac function and pulmonary congestion could not be effectively improved, the anti-infection effect would be significantly affected [27]. Finally, this comprehensive treatment had achieved significant results, and severe infections could be effectively controlled under severe neutrophils shortage. Hematopoietic reconstitution was achieved at 14 days after transplantation. Complications after transplantation such as CMV antigenemia and hemorrhagic cystitis were effectively controlled after active treatments.

In this case, a SAA patient was treated with HLA-haploidentical transplantation combined with unrelated BMSC infusion. During the pre-treatment, patient encountered multiple organ failures and severe infections, but was successfully rescued and the transplantation was also successful. Red blood cell injection was discontinued at 42 days after transplantation, when the hemogram was stable. Serious GVHD did not occurred in the patient. This suggests that Haplo-HSCT combined with unrelated BMSC infusion has a significant curative effect and safety in SAA patient. In clinical practice, this approach has a positive significance of expanding the scope of donors and improving the treatment level of blood diseases.

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#### Disclosure of conflict of interest

None.

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