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Clinical applications of haploidentical hematopoietic stem cell transplantation in severe aplastic anemia

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Abstract. – OBJECTIVE: The purpose of this study was to investigate the efficacy and safety of haploidentical allogeneic hemopoietic stem cell transplantation (allo-HSCT) in severe aplastic anemia (SAA) and prophylaxis of complications involved.

PATIENTS AND METHODS: 8 patients with clinically diagnosed SAA (5 cases of SAA-I and 3 cases of SAA-II) were recruited, with the parents as the donors of hemopoietic stem cells. The conditioning regimen before HSCT included cyclophosphamide, fludarabine, pig anti-human lymphocyte immune globulin (p-ALG) and/or total body irradiation (TBI). The recipients received short-term methotrexate (MTX), mycophenolate mofetil (MMF), and cyclosporin A (CsA) for graft *versus* host disease (GVHD) prophylaxis. Subsequent to successful allo-HSCT, the hematopoietic reconstitution was observed, coupled with periodical surveillance of the chimerism rate, the occurrence, and severity of postoperative complications as infection, GVHD, veno-occlusive disease (VOD), hemorrhagic cystitis (HC), cytomegalovirus (CMV) as well as the long-term survival rate, etc.

RESULTS: We found that hematopoietic reconstruction was achieved in all of the 8 patients with the average time of 14.8d for absolute neutrophil count (ANC) > 0.5×10^9/L, and the average time of 15.0d for platelet count was more than 20×10^9/L. Follow-up for 1 month later revealed that DNA chimeric rate of donor cells was 95%-100%. The complications were aGVHD in 7 cases including 5 cases of grade I-II (62.5%), 1 case of grade III (12.5%) and 1 case of grade IV (12.5%), as well as chronic graft versus host disease (cGVHD) in 2 patients, including 1 case (12.5%) localized in the oral cavity and 1 case (12.5%) with extensive type cGVHD in the whole body skin. No VOD or HC was observed, and no transplantation-related death occurred at median following-up of 8.5 months (2 to 18 months).

CONCLUSIONS: Allo-HSCT is safe and effective in patients with SAA and has great clinical perspective.

Key Words:
Severe aplastic anemia, Hematopoietic stem cell transplantation, Haploidentical hematopoietic stem cell transplantation.

Introduction

The severe aplastic anemia (SAA) is a kind of disease involving bone marrow stem cells injury and hematopoietic microenvironment abnormality resulting from physical, chemical and biological factors and unknown causes followed by the replacement of blood-forming marrow by adipose tissues and cells decrease. The SAA can happen at widely different ages mainly among children and young patients, and the conventional immunotherapy approaches based on cyclosporin A (CsA) adopted by the majority of domestic hospitals in the past are characteristic of slow effect, low efficiency and poor prognosis. Although the immunosuppressive therapy based on antithymocyte globulin (ATG) and cyclosporin A greatly improves the survival rate of SAA patients, only 40%-60% of patients can have their hemogram recovered, and the efficacy of the said therapy approach can only be evaluated after about 6 months, and the effect of treatment still needs improving. Compared with the immunosuppressive therapy (IST), allogeneic hemopoietic stem cell transplantation allo-HSCT is characteristic of rapid hematopoietic reconstitution, low recurrence rate, high failure free survival rate, and less secondary malignant tumors. Because the majority of families have only one child in China, only 30% of patients can find a HLA-matched donor, and such percentage is even lower among adolescent patients and children patients. It is more challenging to find unrelated donors; thus, the majority of

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patients fail to be effectively treated due to time and sources restrictions. Haplo-HSCT can search for unrelated donors without the need to wait for the donors from bone marrow bank, and almost all patients can rapidly find haplotype-matched related donors, and also the preparation time is only 1-2 weeks, thus, greatly reducing the costs spent for bone marrow bank search. Therefore, our department will apply Haplo-HSCT to the clinical treatment of SAA patients and will make a primary research on its efficacy.

Patients and Methods

Patients

The haploidentical allogeneic hemopoietic stem cell transplantation was applied to 8 SAA patients in the Hematology Department of Xuzhou Central Hospital from June 2014 to December 2015. Among those cases, there were 5 male patients and 3 female patients, and the age range of which was within 5-26 years old, and the median age of patients was 14 years old. The medical history of 8 patients lasted for 2 months-6 years. Among the 8 patients, there were 5 patients with SAA-I and 3 patients with SAA-II. The patient with the longest medical history was injected with erythrocyte and platelet concentrate suspended for more than 10 times. All patients were checked in terms of blood routine, bone marrow morphology, bone marrow biopsy pathology, and chromosomal karyotype analysis in accordance with the diagnostic criteria of SAA as specified in the third edition of *Diagnosis and Therapeutic Effect Criterion of Blood Disease*[1]. All donors were parents of patients with age range within 25-52 years old and the median age of 37 years old. The patients were given physical examination and found qualified for donating hemopoietic stem cells. The locus of A, B, C, DR, DQ of donors were given high-resolution molecular biology matching, among which there were 4 donors of 5/10 match, 3 patients of 6/10 match and 1 patient of 7/10 match. There were 5 blood-compatible patients, 1 major incompatible patient and 2 minor incompatible patients (Table I).

Stem Cell Mobilization, Collection and Transplantation Type

5-10 μg/(kg.d) of recombinant human granulocyte colony-stimulating factor (rhG-CSF) is applied to donors to carry out stem cells mobilization, and total dosage of which was divided into 2 times a day, and the hypodermic injection was implemented for 5-6 days. In the fifth day, the COBESpectra (produced by Gambro BCT Company, Lockwood, CO, USA) was adopted to separate peripheral blood stem cells, and the circulating blood volume was 8-12L for each time. In the sixth day, 300-800 ml bone marrow stem cells were collected from posterior superior spine after the local anesthesia was given to patients in a bioclean environment, and CD34+ was counted and transported back to the patients by adopting the parallel flow cell sorter so as to ensure mean neutrophil count (MNC) >5.0×108/kg, CD34+cell population >2.0×10^6/kg. The hydroxyethyl starch was adopted to sediment red cells as for the major compatibility of ABO blood type, and the blood plasma was removed as for the minor compatibility of ABO blood type. All patients were treated with mixed transplantation of peripheral blood stem cells and bone marrow.

Pretreatment Scheme

6 patients were treated with the regimen of cyclophosphamide (CTX)+fludarabine (Flu)+ antilymphocyte globulin (ALG, pig): Cy 50 mg.kg-1.d-1×4d (-5d/-2d), Flu 25-30 mg. kg-1.d-1×4d (-8d/-5d), ALG 25 mg. kg-1.d-1×5d (-5d/-1d). 2 patients were treated with Cy+Flu+ALG+total body irradiation (TBI). The total body irradiation was applied to patients based on the above-mentioned dosage, and the total dosage was 2-3Gy, and the eyes and testes of patients were covered upon irradiation.

Prevention and Supportive Treatment of Transplantation Complications

Patients started to be treated in class 100 laminar ward and to have disinfection diet from pretreatment. The fluconazole or itraconazole was adopted to prevent fungal infections. The ursodeoxycholic acid + prostaglandin E and low molecular heparin calcium were adopted to prevent veno-occlusive disease (VOD), and the patients were stop having low molecular heparin calcium until the blood platelet count ≤20×10^9/L. The ganciclovir or acyclovir failed to be used in 4 patients to prevent cytomegalovirus (CMV) infection, and CMV-DNA and Epstein-Barr virus (EBV)-DNA were tested weekly after the transplantation. ALG + CsA + mycophenolate mofetil (MMF) + short course methotrexate (MTX) prevention aGVHD was adopted as below. The CsA 2.5 mg/(kg.d) was applied to patients in -7 days, and CsA blood concentration was tested weekly, and patients were given the medicines orally until the intestinal function was recovered, and

Table I. Clinical characteristics of patients and donors.

Case No	Age (year)	Sex	Diagnosis Recipient/Donor	Relationship Recipient/Donor	Blood group	HLA-matched
1	Six years and nine months old	Male	SAA-II	son/father	O/O	5/10
2	Eight years and three months old	Male	SAA-II	son/mother	A/A	6/10
3	Fourteen years old	Female	SAA-I	daughter/mother	AB/B	7/10
4	Twenty six year old	Female	SAA-I	daughter/father	A/A	5/10
5	Twenty one year old	Male	SAA-I	son/father	B/O	5/10
6	Fifteen years old	Male	SAA-I	son/mother	O/O	6/10
7	Four year and eight months old	Female	SAA-I	daughter/mother	O/A	5/10
8	Sixteen years old	Male	SAA-II	son/mother	A/A	6/10

the blood concentration was maintained at the level of 150-200 μg/L generally, and MTX (+1, +3, +6, +11d) was applied to short treatment course together with MMF. The compound sulfamethoxazole tablets were adopted to prevent *Pneumocystis carinii pneumonia*. The donors were given medicines of sodium bicarbonate, dexamethasone, and promethazine before being injected with stem cells. If the patients suffer from concurrent infection during the transplantation for lack of granule cell, the broad-spectrum antibiotics combined with antifungal agents was adopted, and the patients were actively injected with blood products going through 25Gy irradiation by γ radial according to the value of blood routine so as to maintain the hemoglobin >80 g/L, blood platelet count $<20\times10^9$/L.

Therapeutic Efficacy Evaluation and Test of Engraftment Evidence

The blood was tested every day or every other day after the transplantation, and absolute neutrophil count (ANC) $>0.5\times10^9$/L, and the blood platelet count (Plt) $\geq20\times10^9$/L for consecutive 3 days, and the patients were not injected with blood platelet for consecutive 7 days as the index for hematopoietic reconstruction. The myelogram was rechecked 1, 3, 6 or 12 months after the transplantation, and the physicians made the judgment on transplantation condition according to the short tandem repeat polymerase chain reaction (STR-PCR). According to STR-PCR detection, cells >95%-100.0% represented complete chimerism of donors, namely the hematopoiesis in the body of patients was completely from donors. The donor cells >2.5%-95.0% represented mixed chimerism, namely the hematopoiesis in the body of patients were both from donors and patients. The donor cells within 0-2.5% represented the hematopoiesis in the body of patients were completely from patients and donor cells are rejected or grated unsuccessfully. The person with blood group incompatibility were analyzed weekly after hematopoietic reconstitution until the blood type turns to the blood type of donors, which means that the transplantation was successful.

Diagnosis and Grading of GVHD

The diagnosis, analysis, and treatment of acute GVHD (aGVHD) and chronic (cGVHD) were conducted in accordance with BSBMT guidebook[2]. aGVHD usually broke out upon the recovery of hematopoiesis after the transplantation, and the early occurrence of aGVHD suggested that the prognosis was poor. The target organs involved in aGVHD usually included the skin, intestinal tract, liver and sometimes may include joints, eyes, etc. The physicians conducted a clinical observation on pruritus, skin rash, diarrhea, abdominal pain, the color and property of the stool, photophobia of eyes, conjunctival hemorrhage, and tested the liver function to intervene the aGVHD in the early period. cGVHD is the main complication and cause of death except for recurrence. The skin, oral cavity, liver and eyes were the parts which were easy to get infected. The local treatment measures were usually adopted to treat with local cGVHD. The generalize cGVHD was impossible to be relieved by itself, so the physicians took comprehensive treatment measures including MMF and FK506 to treat with the generalized cGVHD.

Statistical Analysis

SPSS13.0 software (SPSS Inc., Chicago, IL, USA) was adopted to carry out statistical anal-

Table II. Result of haplo-HSCT in 8 cases of severe aplastic anemia.

Case No	MNC cell ($\times10^8$/kg)	CD34+ cell ($\times10^6$/kg)	Time of ANC > 0.5×10^9/L	Time of Plt > 20×10^9/L	aGVHD	VOD	HC	CMV-DNA	Survival time (month)
1	15.27	6.69	+17d	+21d	II	none	none	(+)	15
2	8.62	3.46	+11d	+13d	II	none	none	(+)	13
3	7.65	2.24	+13d	+18d	II	none	none	(+)	18
4	5.14	2.21	+16d	+16d	0	none	none	(+)	7
5	9.90	2.10	+11d	+15d	III	none	none	(+)	7
6	11.01	2.87	+17d	+11d	I	none	none	(–)	4
7	13.20	5.66	+13d	+11d	IV	none	none	(+)	2
8	7.64	8.96	+20d	+15d	II	none	none	(+)	2

MNC: mononuclear cells; ANC: absolute neutrophil count; Plt: platelets

ysis; the means comparison was tested by the independent sample t, the comparison of sample rate was tested by χ^2, and $p<0.05$ shows that the difference has statistical significance. The Kaplan-Meier method was adopted to carry out survival analysis and single factor analysis, and the follow-up visits were conducted until December 31, 2015. $p<0.05$ was considered statistically significant.

Results

Complications During the Pretreatment

During the pretreatment period, all patients suffered from the mild gastrointestinal reactions, including nausea, emesis, etc., and there were 3 patients with different degrees of infection, and all patients improve markedly after being given active symptomatic and supportive treatment. There were no patients suffering from organ function lesions. The two total body irradiation (TBI) patients did not have any post-radiation complications including swelling parotid gland, pains etc.

Reconstruction of Hemopoietic Stem Cells

8 patients have had their hemopoietic stem cells reconstructed, and mononuclear cells (MNC) median of injected donor stem cells was 9.80 (5.14-15.27) $\times10^8$/kg, and the median of CD34+ was 4.27 (2.10-8.96)$\times10^6$/kg. The median time for the engraftment of transplanted granulocyte was 14.8 (11-20) days, and the median time for the engraftment of blood platelet was 15.0 (11-21) days respectively. The chimerism conditions of patients were rechecked 1 month after the transplantation, and DNA chimerism rate of donor cells was within 95%-100%. Where the blood type of donors was different from that of patients, their blood type was transformed into the blood type of donors after the transplantation. The transplants in 3 patients were rejected 3 months after the transplantation, and the chimerism rate reduced as low as 72% as well as the peripheral blood cell. The chimerism rate rebounded to 85%-100%, and the blood routine returned to the normal level after the patients were injected with donors' bone marrow blood (Table II).

Occurrence of GVHD

There were 7 patients suffer from a Graft *Versus* Host Disease (GVHD), among which 5 patients (62.5%) suffered from aGVHD of I-II degree, 1 patient (12.5%) suffered from aGVHD of III degree and 1 patient (12.5%) suffered from aGVHD of IV degree. There were 3 patients (37.5%) who had their skin involved and 4 patients (50.0%) who had their intestinal tracts involved. There were 1 patient (12.5%) suffer from oral cavity-located cGVHD, and the main symptoms may include oral pain, oral lichenoid lesions and oral ulcer difficult to be healed. There were 1 patient (12.5%) suffer from generalized cGVHD, and the main symptoms may include pruritus and lichenoid lesions. Upon the occurrence of aGVHD, the patients shall be injected with 1-2 mg/(kg.d) methylprednisolone (MP) in the veins, and the dosage of methylprednisolone was reduced after it takes effect until the patients stop taking the given medicine. If the medicine did not take any effect, CSA was replaced by FK506 treatment or added with CD25 monoclonal antibody treatment. cGVHD was usually treated by the method of monotherapy or combination

therapy, including local treatment, methylprednisolone, cyclosporine or FK506 and other medicines, FK506 was taken by patients orally as per 0.1 mg/(kg.d), and the blood concentration was maintained at the level of 5-10 μg/L, and GVHD occurred to patients was controlled to different extents after active treatment (Table II).

Other Post-transplantation Complications and Follow-up Visits

After the transplantation, all patients suffered from no hepatic vein occlusion syndromes, hemorrhagic cystitis, and interstitial pneumonia. 8 patients suffered from different degrees of infection and fever, and body temperature of patients began to recover to the normal level after being treated with broad-spectrum antibiotic, vancomycin and antifungal therapy. There were 7 patients suffer from cytomegalovirus (cytomegalovirus, CMV) and EB viremia (Epstein-Barr virus, EBV) among 8 patients. For the 7 patients with transplanted their lungs, intestinal tracts and other organs, etc., blood CMW or EBV was tested to be within the normal level after the patients were treated with ganciclovir or acyclovir. There were 2 patients suffer from oral mucositis of II-III degree, and the symptoms began to improve after the patients were treated with comprehensive treatment methods, including oral nursing, physiotherapy, kangfuxin lotion, rhGM-CSF mouthwash, recombinant human epidermal growth factor, etc. Two patients suffered from epilepsy during the process to take FK506, and patients improve after replacing FK506 with CsA. The median follow-up time was 8.5 months (2-18 months), during which there was no transplantation-related fatality (Table II).

Discussion

SAA, a serious failure of bone marrow haematopoietic function caused by varied reasons is characterized by acute occurrence, serious conditions, poor treatment response, and high mortality rate[3]. At the present stage, ATG together with CsA (an immunosuppressive) and HSCT are the main measures to treat SAA[4]. However, the immunosuppressive therapy has a slow onset, and most of the patients in the treatment process can only be out of the blood transfusion temporarily and easy to cause serious infection[5], it increases more economic expenditure. HSCT can provide hematopoietic stem cells and mesenchymal stem cells for patients with SAA and correct the disorder of the immune system for providing efficient treatment for SAA[6]. Based on China's national conditions and the characteristics of the development of the disease, in only a small number of cases the sibling matched donors were found on time for the treatment[7]. Chinese bone marrow bank needs a long time to look for an unrelated donor, resulting in large transplantation risk comparatively. To expand the source of the donor, Haplo-HSCT is becoming a hot spot of research in recent years[8]. Haplo-HSCT's main risk lies in the difficult transplantation, after transplantation the incidence of infection and GVHD are high, and the immune function recovery delays, etc. All of these restrict the clinical application of the SAA treatment[9].

To overcome the difficulty of transplantation, several studies have been conducted. As reported by Wang et al[10], haplotype hematopoietic stem cell transplantation has been carried out on 17 children and adolescents with SAA. The median time to implant the neutrophil insertion in place was 16 days, the time of platelet 22 days. The prevalence rate of aGVHD in the second to fourth degree in more than 100 days was 30.53 ± 11.12%, and the third to fourth-degree aGVHD only occurred to one patient. The occurrence rate of cGVHD was 21.25 ± 13.31%. The overall survival rate was 71.60 ± 17% in the median follow-up of 362 days (36 to 1321 days), indicating that haplotype hematopoietic stem cell transplantation is feasible and can be a salvage therapy for children and adolescents with SAA deficiency. As the domestic transplant center reports[11], in the treatment of blood haploidentical transplantation for the SAA patients, there were 15 survival cases among 21 patients with the survival rate of 71.4% in the median follow-up 16 (3-46) months. It confirmed that HLA the blood haploidentical stem cell transplantation for treatment of SAA is safe and effective. It can be seen that the blood haploidentical HSCT solves the problem of donor source, the implantation success rate is satisfactory, and the complications after transplantation can be well controlled.

Through the patients' previous follow-up observation and statistical analysis, we found that the blood haploidentical HSCT has certain advantages in the treatment of patients with the malignant hematologic disease[12]. Based on the successful treatment of haploidentical HSCT of leukemia and other malignant hemopathy

patients, since from 2014 we explored treatment gradually by using haploid HSCT for our SAA patients. In donor selection, if there was no matched donor blood cell, the relative haploid transplantation was selected which can win the opportunity to find a complete cure for the disease and the donor stem cell source was convenient with no risk of regretting donation. If the transplanted stem cells were transplanted into the patient imperfectly, the bone marrow stem cells were taken out more times in a timely manner to the patients so the implantation rate can be improved. Based on the classical CTX+ALG, preprocessing scheme added the use of fludarabine and TBI, which can not only increase the intensity of immunosuppressive, but also help promote implantation and alleviate GVHD. The transplantation methods were determined to be mixed transplantation of G-CSF mobilized bone marrow and peripheral blood stem cell, which contained a large number of hematopoietic stem cells and a certain amount of bone marrow stroma cells to accelerate hematopoietic reconstitution and significantly reduce the incidence of severe GVHD. To save the cost of patients, we implemented local anesthesia to the donor with family difficulties under the sterile and monitoring environment and repeat extraction of bone marrow from posterior superior iliac crest with less puncture point. The results showed that the donor's pain was small, and appropriate reduction of the donor's bone marrow collection did not affect the patients' smooth hematopoietic reconstruction, which explored a new way of bone marrow collection for the economically underdeveloped areas. Before transplantation, given an intramuscular injection of long-acting riboflavin, only two cases had oral mucositis inflammation of II-III degree. After active and symptomatic treatment, the rapid recovery showed that the prevention method was effective. The department adopted Alprostadil Injection + ursodeoxycholic acid + low molecular weight heparin calcium (PLT $<20\times10^9$/L disabled) to prevent VOD. All 8 patients did not show VOD, suggesting that the application of alprostadil injection 10 μg once daily was sufficient and ursodeoxycholic acid had a more important role for VOD prophylaxis. There was no HC in all 8 cases after patients got adequate hydration, alkalization, mesna application and forced diuresis. Among 8 cases of patients, 7 appear blood CMV-DNA and EBV-DNA copy number increased after transplantation. Considering that in some cases preventing the effects of drugs on blood cells, the use of ganciclovir prophylaxis was not adopted. Other explanation could be that hospital laboratory detection methods were too sensitive, with ganciclovir and acyclovir antiviral therapy, none of the patients had appeared CMV disease. For the prevention of GVHD, we adopted traditional CSA+ small dose MTX+ALG, by using CSA 7 days in advance. After giving sufficient CSA and detecting plus maintaining the concentration of CSA, most patients did not have severe GVHD. If GVHD does appear, enough methylprednisolone and FK506 should be applied, and refractory of intestinal GVHD should be treated by CD25 monoclonal antibody in a timely manner. The patients were improved, and pretreatment with pig ALG instead of rabbit ATG the effect was acceptable, which were successfully implanted and severe GVHD does not occur after transplantation, with expenditure reduced significantly. The EBMT-SAA working group through more than 100 cases demonstrated that the patients have a higher long-term survival rate with a low dose of total body irradiation for SAA patients[13]. So there were 2 patients to whom we have taken the TBI pretreatment methods, and achieved good results. After transplantation through of STR-PCR and blood routine test, when the chimeric rate, white blood cell count and platelet count were found to decline, 2-3 ml/kg unused donors' bone marrow blood was infused once timely, 1-2 times a week, for 2-3 times consecutively, which of great help to promote stable stem cell implantation. In the 19 cases treatment of refractory SAA by Haplo-HSCT therapy exercised by Xu et al[14], all patients were successfully implanted, and the occurrence of aGVHD, the control, and long-term survival rate were more satisfying showing the reliability of the haploid transplantation.

Conclusions

Due to the current use of foreign the blood haploidentical HSCT for SAA is still less, the study group only explored a smaller number of cases preliminary, and patients were followed up for a short time. But the completed follow-up observation of HSCT for SAA patients showed that without HLA All-matched donor, it was safe, effective and worth promoting for the treatment of SAA patients.

Conflict of interest

The authors declare no conflicts of interest.

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