Allogeneic Hematopoietic Stem Cell Transplantation for Children with Severe Aplastic Anemia

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Objective: *Allogeneic hematopoietic stem cell transplantation (allo-SCT) is a potentially curative treatment for severe aplastic anemia (SAA). This is a single institutional review to study the feasibility of using allo-SCT for Thai children with SAA.*
Material and Method: *Nine children with SAA (7 matched-sibling donor-SCT, 1 matched-unrelated donor-SCT and 1 haplo-identical-SCT) underwent allo-SCT between October 2002 and September 2010. Cyclophosphamide and anti-thymocyte globulin (CY/ATG) were used as conditioning regimen for 4 patients with matched-sibling donor-SCT. CY/ATG and fludarabine were used for 3 patients with matched-sibling donor-SCT and one patient with haplo-identical SCT. One matched-unrelated donor-SCT received CY/ATG and total body irradiation.*
Results: *Eight of 9 patients (89%) achieved neutrophil engraftment within 13.5 days (range 6.0-22.0). One matched-sibling donor-SCT recipient who failed to achieve engraftment died from acute renal failure and gram-negative sepsis on day 21 post allo-SCT. One matched-sibling donor-SCT case developed late graft failure on day 72 and died from invasive fungal infection. For graft versus host disease (GVHD), a haplo-identical-SCT patient died from steroid refractory grade IV acute GVHD. At last follow-up, six patients (67%) alive at a median follow-up time of 76.4 months (range 2.3-88.8). Overall survival (OS) and event-free survival (EFS) at 5 year was 63% and 65%, respectively.*
Conclusion: *Allo-SCT is a feasible curative treatment for children with SAA in Thailand. Graft failure and severe GVHD in alternative donors SCT are responsible for major causes of death. OS and EFS probabilities are stable after the first year post transplant.*

Keywords: *Allogeneic stem cell, Stem cell transplantation, Aplastic anemia, Children*

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Children and adolescents are the most commonly affected age group of severe aplastic anemia (SAA). Without definite treatment, infections and hemorrhage are the leading causes of death. Allogeneic hematopoietic stem cell transplantation (allo-SCT) is an effective treatment for SAA although with limitation to find the suitable HLA-matched donor. Cyclophosphamide (CY) and anti-thymocyte globulin (ATG) are frequently used as the preparative regimen. The unique property of CY is an immunosuppressive agent with stem-cell sparing effect[1]. In heavily transfused patients who are likely to develop graft rejection, an addition of ATG during conditioning revealed improved engraftment and lengthened survival[2]. Total body irradiation (TBI) combined with ATG resulted in more promising outcome in terms of increase treatment failure-free survival for unrelated donor allo-SCT. On the other hand, high dose TBI is associated with worse pulmonary complications[3]. In this regard, fludarabine in place of TBI is more tolerable in recent publications[4-6]. With accumulating knowledge and skill to treat patients with SAA, the authors therefore review our institutional outcome of allo-SCT for children with SAA. The purpose of this report is to study survival, graft rejection rate, transplant-related complications, graft-versus-host disease of SAA patients who underwent

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allo-SCT at Ramathibodi Hospital, Mahidol University since 2002.

Material and Method

Patients

Between October 1, 2002 and September 30, 2010, 9 patients with SAA received allogeneic hematopoietic stem cell transplant at Ramathibodi Hospital. SAA defined by Camitta Criteria as bone marrow cellularity less than 25% with 2 of the following 3 laboratory abnormalities: absolute neutrophil count less than 0.5 x 10^9/L, platelet count less than 20 x 10^9/L, and an absolute reticulocyte count less than 50 x 10^9/L. Exclusion criteria included other underlying hematologic diseases, myelodysplasia, Fanconi anemia and other congenital aplastic anemia. Informed consent for study participation approved by Institutional Review Board of Ramathibodi Hospital had been provided by legal guardians of all patients.

Patient characteristics are shown in Table 1. There were 8 males and one female. Median age at allo-SCT was 11 years (1.9-15.9). Median period from diagnosis to allo-SCT was 0.9 year (0.1-2.5). One patient had paroxysmal nocturnal hemoglobinuria (PNH) at the time of SAA diagnosis. In terms of SAA treatment, 4 patients received cyclosporine, ATG, corticosteroids, and oral metenolone enanthate. Three received corticosteroids and oral metenolone enanthate. Two patients received only blood and platelet transfusion without medication.

Table 1. Characteristics of patients and HSCT

Variable	n (%)
Number of subject	9 (100)
Male/female	8/1
Years of HSCT	
2002-2005	6 (67)
2006-2010	3 (33)
Donors	
Matched sibling	7 (78)
Matched unrelated	1 (11)
Haplo-identical	1 (11)
Graft type	
Bone marrow	5 (56)
PBSC	4 (44)
Infused cell dose (x 10^8/kg)	5.0 (2.2-10.7)
Conditioning regimen	
CY + ATG + fludarabine	4 (44)
CY + ATG	4 (44)
CY + ATG + TBI	1 (11)
GVHD prophylaxis	
CSA + MTX	5 (56)
FK 506 + MTX	3 (33)
CSA + MMF	1 (11)
Donor-recipient sex match	
Male to male	3 (33)
Male to female	1 (11)
Female to female	0 (0)
Female to male	5 (56)
Blood type between donor-recipient	
Match	6 (67)
Major	3 (33)
Minor	0 (0)
Median days of neutrophil engraftment (day)	13.5 (range 6.0-22.0)
Median days of platelet engraftment (day)	22.0 (range 6.0-24.0)
Median follow-up of survivors (month)	76.4 (range 2.3-88.8)

Donor selection

HLA matched-sibling was used as allo-SCT donors for 7 patients (78%). For patients without matched-sibling donor (MSD), one was transplanted from haplo-identical father (11%) and the other from matched unrelated donor (MUD) peripheral blood stem cell (11%).

Transplantation procedure

Four patients (44%) received CY (50 mg/kg for 4 days) and rabbit ATG (10 mg/kg of Fresenius Kabi rabbit anti-thymocyte immunoglobulin for 4 days). Other four patients (44%) received same dose and schedule of CY and ATG (CY + ATG) with fludarabine (30 mg/m^2 for 6 days). Only one unrelated donor allo-SCT recipient (11%) received CY + ATG with TBI (250 cGy/fraction every 12 hours for 4 fractions). Intravenous 2-mercaptoethane sulfonate (Mesna 10 mg/kg) for prophylaxis of hemorrhagic cystitis was given 30 minutes before and 3, 6 and 9 hours after CY infusion. Bone marrow (BM) or peripheral blood stem cells (PBSC) were infused as a stem cell source with a minimum of 10^8 nucleated cells per kilogram. Median CD34 cell dose was 5.0 x 10^6 cells/kg of recipient body weight.

During the transplant, all patients were hospitalized in an isolation room with HEPA-filtration. G-CSF (5 mg/kg) was given daily from the infusion day until absolute neutrophil count (ANC) was above 1.5 x 10^9/L for 3 consecutive days. Oral acyclovir, ciprofloxacin, penicillin and itraconazole were administered prophylactically throughout the transplant period till day 100. Transfusion support consisted of packed red blood cells and platelets to maintain hemoglobin above 8 g/dL and platelet count above 20 x 10^9/L, respectively. Monitoring of CMV and EBV viral reactivation was performed weekly using real-time PCR for first 3 months after allo-SCT then monthly until 6 months post-transplantation.

For prophylaxis of graft versus host disease (GVHD), 5 patients (56%) received Cyclosporine A (CSA 3 mg/kg twice daily from day -2) and short-term methotrexate (MTX 5 mg/m^2 on day 1, 3, 6 and 11 after marrow infusion). CSA blood level was maintained at 200-400 ng/mL. Three patients (33%) received tacrolimus (FK 506) 0.03 mg/kg continuous infusion from day -2 and short-term MTX. FK 506 blood level was maintained at 5-15 ng/mL. One patient with unrelated donor allo-SCT (11%) received CSA and mycophenolate-mofetil (MMF 30 mg/kg from day 1). GHVD prophylaxis medication was continued at least 6 months post transplant. Acute and chronic GVHD were diagnosed and graded according to standard criteria[7,8]. Neutrophil engraftment was defined as the first of 3 days with ANC greater than 0.5 x 10^9/L. Platelet engraftment was defined as the first of 3 days with platelet count greater than 20 x 10^9/L without platelet transfusion. All cases were tested for chimerism using fluorescence *in situ* hybridization (FISH) probes for sex-mismatched pairs or short tandem repeats of polymorphic DNA sequences for sex-matched pairs.

Statistical analysis

Overall survival (OS) was defined as the time between stem cell infusion date until death or last follow-up. Event-free survival (EFS) was defined as survival without treatment failure. Graft rejection, disease recurrence and requirement of further immunosuppressive agents or second transplant were considered as treatment failures. Complete remission (CR) was defined as achieving normal peripheral blood count without transfusion. Survival probabilities for OS and EFS were estimated using Kaplan-Meier method.

Results

Engraftment and chimerism studies

Eight of 9 patients (89%) achieved neutrophil engraftment. Seven of 9 patients (78%) achieved platelet engraftment. Median days of neutrophil and platelet engraftment was 13.5 (range 6.0-22.0) and 22.0 (range 6.0-24.0) days, respectively.

One MSD-SCT recipient who failed to achieve engraftment died on day 21 post transplant due to acute renal failure, *Pseudomonas aeruginosa* and *Escherichia coli* sepsis. Another patient with haplo-identical-SCT achieved engraftment on day 14 but suddenly developed graft rejection on day 16. Donor lymphocyte infusion (DLI) with CD3 14.2 x 10^7 cells/kg was infused on day 22 followed by a second bone marrow transplant (BMT) with CD34 selection at a dose of 2.3 x 10^6 cells/kg from the same donor on day 43.

One MSD-BMT case developed late graft failure. Mixed chimerism was observed on day 72. DLI with CD3 1.4, 1.3, 2.9, 2.2 and 1.3 x 10^7 cells/kg was infused on day 100, 120, 134, 151 and 169 followed by second BMT with 2.3 x 10^6 cells/kg infused cell dose on day 175 after the first transplant. However, this patient never achieved complete donor chimerism and finally died from fulminant disseminated candida infection and persistent pancytopenia.

Chimerism studies were performed in all cases. Six patients who were alive at the end of study achieved

complete donor chimerism.

Graft versus host disease (GVHD)

Two patients in the present study developed acute GVHD. One of 7 patients with MSD allo-SCT developed grade II acute GVHD presented with diarrhea and hepatitis on day 47. This patient was successfully treated with methylprednisolone, MMF, increased dose of FK 506, and 50 mg of daclizumab (Zenapax) for 3 doses. After recovery from acute GVHD, all medications were gradually discontinued without recurrence of symptoms or presence of chronic GVHD.

A haplo-identical-SCT patient developed steroid resistant grade IV GVHD on day 64 with manifestations of severe diarrhea and lower gastrointestinal hemorrhage. With continuation of FK 506, MMF and anti-TNF-alpha receptor antibody (inflizimab) were added to control GVHD. Despite successful engraftment, this patient died from severe acute GVHD, *Escherichia coli*, *Streptococcus* gr D and *Enterococcus* spp. sepsis.

Mild chronic skin GVHD was observed in a patient who underwent MUD-SCT. This patient received CY/ATG for conditioning and CSA/MMF for GVHD prophylaxis. Initially this patient presented with grade I steroid resistant skin and gut acute GVHD. From this reason, ATG was also given. This patient eventually developed limited chronic skin GVHD which was successfully treated with additional FK 506.

Viral infection

CMV reactivation was observed in one of 9 patients. Gancyclovir was administered as well as discontinuation of immunosuppressants. No EBV reactivation was observed in the present study. Two cases developed hematuria which BK virus was identified. One patient developed respiratory syncytial virus (RSV) and adenovirus pneumonia.

Fungal infection

As mentioned earlier, one MSD-BMT patient with late graft failure developed disseminated candida infection at lung and liver. Although with administration of intravenous liposomal amphotericin B, this patient eventually deceased.

OS and EFS

Six of 9 patients (67%) were alive without disease at a median follow-up time of 76.4 months (range 2.3-88.8). Death was observed in 2 MSD-SCT recipients and one paternal haplo-identical-SCT recipient owing to graft failure. Treatment failure included 2 patients with primary graft failure and one patient with late graft failure. The OS and EFS at 5 year was 63% and 65%, respectively (Fig. 1 and 2).

Discussion

Allogeneic stem cell transplantation (allo-SCT) from a matched sibling donor is a curative treatment for children with severe aplastic anemia (SAA). Long-term overall survival (OS) had been reported in 80%-90% of children and minimally transfused young adults[9]. Favorable predictors for survival in the European Group for Blood and Marrow Transplantation Severe Aplastic Anemia Working Party

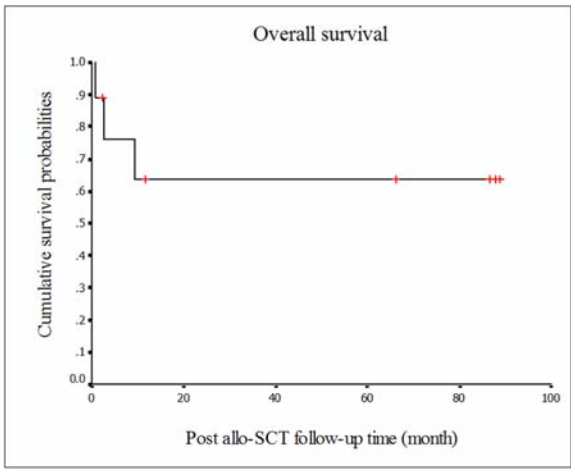

Fig. 1 Overall survival of SAA patients post allo-SCT. Tick marks indicate surviving patients

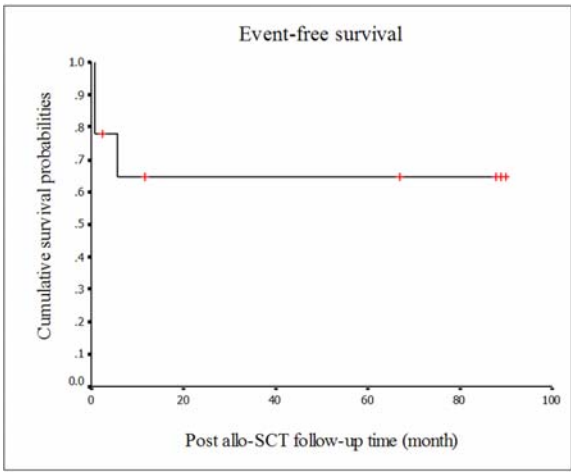

Fig. 2 Event-free survival of SAA patients post allo-SCT. Tick marks indicate surviving patients

(SAA-WP, BMT) published data included young age, underwent allo-SCT after 1996, matched sibling donors, short interval between diagnosis and transplant and no TBI in the conditioning regimen[10].

Serious complications following allo-SCT are graft failure and graft-versus-host disease (GVHD). Graft rejection occurred in 5%-15% of matched sibling allo-SCT for adults with SAA. One of significant risk factors for graft rejection was heavy transfusion prior to the transplant[11].

In the present study, OS at 5-year was 63%. Major cause of death in these 3 patients was graft failure which was detected at day 16, 21 and 72 after allo-SCT. Two received MSD bone marrow in doses of 3.1 and 10.7 x 10^8 nucleated cells per kilogram. One received paternal haploidentical PBSC in a dose of 4.5 x 10^8 nucleated cells per kilogram. From these, the authors are able to exclude insufficient infused nucleated cell dose as a cause of graft failure. However, all of them were diagnosed SAA and referred from other hospitals. The authors have very limited data regarding number of red blood cells and platelets transfusion prior to allo-SCT.

According to preparative regimens, the most frequent used in the present study are Cyclophosphamide plus ATG (CY + ATG) and Cyclophosphamide/ ATG plus fludarabine (CY + ATG + fludarabine). Only one patient who received matched unrelated BM was additionally given TBI. Due to small number of patients enrolled, the authors cannot compare an efficacy of each regimen. The current most widely used preparative regimen for HLA-matched sibling allo-SCT is high dose cyclophosphamide plus ATG. TBI-based regimen has been abandoned in SAA due to increasing adverse results of chronic GVHD and second malignancy[12]. More recent study describes a new conditioning regimen consisting of low dose Cyclophosphamide, ATG, and fludarabine which has shown lower rates of GVHD and treatment related complications[13]. Moreover, higher rates of engraftment and survival were observed in Cyclophosphamide plus fludarabine, with or without ATG even in heavily transfused patients[14]. At this stage, benefit of using fludarabine to improve engraftment rate still requires more investigation.

Various immunosuppressive agents were used for GVHD prophylaxis in SAA transplantation. For matched sibling transplant, CSA + MTX showed a slight, non-statistically significance difference in developing grade II-III acute GVHD versus CSA alone (30% and 38%, respectively)[15].

Because only 30% of patients have a suitable donor, mismatched family members and unrelated donors are considered for allo-SCT. Nonengraftment and severe GVHD rates increased with uses of alternative donors[16]. More aggressive immunosuppressive agents such as FK 506 and MMF have been shown to be effective for GVHD prophylaxis. From matched-pair analysis comparing FK 506 + MTX with CSA + MTX in patients with SAA given URD-SCT, no statistically significant difference in probabilities of acute and chronic GVHD was detected. This Japanese study shows only the superiority of FK 506 + MTX over CSA + MTX in overall survival because of the lower incidence of transplant-related deaths[17]. Infection-related mortalities in the present study were apparently associated with graft failure and severe GVHD which required elevated doses of immunosuppressive agents. Patients who underwent allo-SCT from alternative donors herein also developed more serious and fungal infections. The mortality rate of MUD-SCT is about twice that observed in matched sibling transplants[9]. A rejection rate of MUD-SCT for SAA is approximately 15%[18]. To identify the optimal preparative regimen for MUD-SCT in severe aplastic anemia, using low dose CY + ATG + fludarabine without TBI revealed a lower rate of acute and chronic GVHD with only 5% graft rejection rate[19]. No available cord transplant was used for SAA in the present study. Umbilical cord blood (UCB) is a potential hematopoietic stem cell option for SAA when no other suitable donors are available. However, this approach is limited by small number of stem cells particularly within a single umbilical cord blood donation.

The authors data support the feasibility of allo-SCT for children with SAA in Thailand. Graft failure and severe GVHD in alternative donors SCT responsible for major causes of death. The OS and EFS probabilities are stable after the first year post transplant. Larger scale and randomized studies are necessary to confirm positive results. Particularly when country resources are limited, outcomes of SAA patients given allo-SCT or immunosuppressive treatment should be compared.

Potential conflicts of interest

None.

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การปลูกถ่ายเซลล์ต้นกำเนิดทางโลหิตวิทยาแบบเอกพันธุ์เพื่อรักษาภาวะไขกระดูกฝ่อชนิดรุนแรงในผู้ป่วยเด็ก

สะการะ หัศภาดล, นงนุช สิระชัยนันท์, อุษณรัสมิ์ อนุรัฐพันธ์, สามารถ ภคกษมา, เดือนธิดา ทรงเดช, อำไพวรรณ จวนสัมฤทธิ์, สมถวิล ศิริเรือง, วันเพ็ญ พันธางกูร, สุรเดช หงส์อิง

วัตถุประสงค์: *ศึกษาผลการรักษาผู้ป่วยเด็กที่มีภาวะไขกระดูกฝ่อชนิดรุนแรงด้วยการปลูกถ่ายเซลล์ต้นกำเนิดทางโลหิตวิทยา*

วัสดุและวิธีการ: *รวบรวมข้อมูลการรักษาผู้ป่วยเด็กที่มีภาวะไขกระดูกฝ่อชนิดรุนแรงด้วยการปลูกถ่ายเซลล์ต้นกำเนิดทางโลหิตวิทยาแบบเอกพันธุ์และนำข้อมูลที่ได้มาวิเคราะห์ทางสถิติ มีผู้ป่วยที่เข้าร่วมการศึกษาทั้งสิ้น จำนวน 9 ราย แหล่งที่มาของเซลล์ต้นกำเนิดมาจากพี่น้องท้องเดียวกัน 7 ราย จากบิดาซึ่งเป็นผู้บริจาคที่มี HLA haplo-identical 1 ราย และจากผู้อื่นที่ไม่ใช่ญาติแต่มี HLA ตรงกัน 1 ราย ผู้ป่วยทุกรายเข้ารับการปลูกถ่ายเซลล์ต้นกำเนิดที่โรงพยาบาลรามาธิบดีในระหว่างปี พ.ศ. 2545-2553 มีผู้ป่วยจำนวน 4 ราย ได้รับยาเคมีบำบัดสูตร Cyclophosphamide และ ATG อีก 3 ราย ได้รับยาเคมีบำบัดสูตร Cyclophosphamide, ATG และ fludarabine ส่วนอีก 1 ราย ซึ่งได้รับไขกระดูกจากผู้บริจาคที่ไม่ใช่ญาติได้รับยาเคมีบำบัดสูตร Cyclophosphamide/ATG และ total body irradiation*

ผลการรักษา: *ผู้ป่วยจำนวน 8 ราย (คิดเป็นร้อยละ 89) เข้าสู่ภาวะ engraftment ในระยะเวลาเฉลี่ย 13.5 วัน มีผู้ป่วยเพียงรายเดียวที่ไม่สามารถเกิด engraftment และเสียชีวิตจากภาวะติดเชื้อกรัมลบและไตวายหลังปลูกถ่ายเซลล์ต้นกำเนิด 21 วัน มีผู้ป่วยรายเดียวซึ่งเกิด graft failure หลังปลูกถ่ายเซลล์ต้นกำเนิด 72 วัน และเสียชีวิตจากการติดเชื้อรา ผู้ป่วย 1 ราย เกิดภาวะ acute GVHD ที่รุนแรงจนเสียชีวิต เมื่อสิ้นสุดการติดตามการรักษามีผู้ป่วยรอดชีวิตทั้งสิ้น 6 ราย (คิดเป็นร้อยละ 67) ระยะเวลาการติดตามการรักษาเฉลี่ย 76.4 เดือน อัตราการรอดชีวิตหรือ overall survival ที่ 5 ปี คิดเป็นร้อยละ 63 ส่วนอัตราการหายขาดจากโรคหรือ event-free survival ที่ 5 ปี คิดเป็นร้อยละ 65*

สรุป: *ในการศึกษานี้พบว่าการปลูกถ่ายเซลล์เซลล์ต้นกำเนิดทางโลหิตวิทยาแบบเอกพันธุ์ได้ผลดีและควรพิจารณาใช้เพื่อการรักษาผู้ป่วยเด็กที่มีภาวะไขกระดูกฝ่อชนิดรุนแรงในประเทศไทย สาเหตุนำของการเสียชีวิตในการศึกษานี้คือ graft failure และ GVHD ที่รุนแรงซึ่งเกิดเฉพาะในผู้ที่ได้รับเซลล์ต้นกำเนิดจากผู้ที่ไม่ใช่ญาติและได้รับเซลล์ต้นกำเนิดที่เป็น HLA haplo-identical อัตราการรอดชีวิตและการหายขาดจากโรคคงที่หลังจากปีแรกที่ได้รับการปลูกถ่าย*