

Characteristics and Outcomes of Severe Aplastic Anemia Patients Who Were Treated with Allogenic Hematopoietic Stemcell Transplantation at Institute Pediatric Hospital Kuala Lumpur during 2003-2012

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Abstract Aplastic anemia is characterized by the development of peripheral blood pancytopenia associated with hypocellularity of the bone marrow. Treatment strategies for aplastic anemia include immunosuppressive therapy and hematopoietic stemcell transplantation. The choice of therapy depends on the severity of the disease, patient's age and availability of a human leukocyte antigen (HLA) matched sibling donor. To describe the clinical characteristics and outcomes of all patients diagnosed with severe aplastic anemia who were treated with allogenic hematopoietic stemcell transplantation at IPHKL. All patients with SAA who had underwent matched sibling hematopoietic stemcell transplantation at IPHKL from January 2002- December 2013 were identified. Retrospective data was collected with regards to patient's characteristics, transfusion history, conditioning regime, time of engraftment, length of stay, complication and outcomes of patients. In this study there were 36 patients with SAA who underwent allogenic hematopoietic stemcell transplantation. Of the 36 patients, 20 (55.6%) were boys and 16 (44.4%) were girls. The most regimes used for conditioning was combination of fludarabine, cyclophosphamide and ATG horse in 19 patients (52.8%). Mostly the granulocyte engraftment at 10 days after transplantation, while platelet engraftment occurred at 12 days after transplantation. Complications that occurred after transplant were febrile neutropenia in 32 patients (88.9%), mucositis in 25 patients (69.4%), fungal infection in 4 patients (11.1%) and only 2 patients had GvHD. No patients died after underwent allogenic hematopoietic stemcell transplantation. Thirty four patients (94.4%) were cured after a single hematopoietic stemcell transplantation, and only 2 patients (5.6%) had late graft rejection, but all were cured after having the second transplantation. The outcomes of patients with severe aplastic anemia who had underwent allogenic hematopoietic stemcell transplantation in bone marrow transplantation ward IPHKL were good. All patients were cured from the disease.

Keywords: severe aplastic anemia, allogenic hematopoietic stemcell transplantation

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1. Introduction

Aplastic anemia is characterized by the development of peripheral blood pancytopenia associated with hypocellularity of the bone marrow. [1,2,3] The clinical presentation is typically due to symptoms associated with thrombocytopenia, anemia and neutropenia. [1,2,3,4]

Aplastic anemia is classified based on the marrow cellularity and the degree of pancytopenia. Diagnostic criteria for severe aplastic anemia include a bone marrow biopsy showing an overall cellularity of less than 25% of the age appropriate for normal cellularity or less than 50% normal cellularity in which fewer than 30% of the cells are hematopoietic. At least two of the followings should also

be present: absolute reticulocyte count <25,000/u/L, absolute neutrophil count <500/u/L or platelet count <20,000/u/L. [1,3,5].

Treatment strategies for aplastic anemia include immunosuppressive therapy and hematopoietic stem cell transplantation. The choice of therapy depends on the severity of the disease, patient's age and availability of a human leukocyte antigen (HLA) matched sibling donor. [6,7,8]

The Bone Marrow Transplant Ward in Institute Pediatric Hospital Kuala Lumpur (IPHKL) Malaysia, started in services in 1994. It is the referral centre for paediatric haematopoietic stem cell transplants for Ministry of Health Hospitals in Malaysia. We report our 10 years experience in transplantation of patients with severe aplastic anemia at our centre from January 2003 until December 2012, to describe the clinical characteristics and outcomes of all patients diagnosed with

severe aplastic anemia who were treated with allogenic hematopoietic stemcell transplantation at Institute Pediatric Hospital Kuala Lumpur.

2. Method

All patients with severe aplastic anemia (SAA) who had undergo matched sibling hematopoietic stemcell transplantation at Institute Pediatric Hospital Kuala Lumpur from January 2002 until December 2013 were identified. Retrospective data was collected from patient's files and ward records with regards to patient's characteristics, transfusion history before transplant, conditioning regime, time of engraftment, length of stay after transplantation, complication and outcomes of patients post transplant. Diagnosis of severe a plastic anemia were made clinically and supported by peripheral blood result and bone marrow aspiration result.

3. Result

From January 2003 to December 2012, thirty six patients with severe aplastic anemia (SAA) underwent allogenic hematopietic stemcell transplantation at Bone Marrow Transplant (BMT) ward, Institute Pediatric Hospital Kuala Lumpur (IPHKL). Of the 36 patients, 20 (55.6%) were boys and 16 (44.4%) were girls. The youngest patient was 1 year 8 months and the oldest was 15 years 7 month of age at the day of transplant. Mean age was 9.4 years.

Most of the races who underwent transplant were Malay, as many as 13 patients (36.1%), followed by Dusun/Peribumi race 12 patients (33.3%), Chinese 6 patients (16.6%), then Iban and Kadazan race 2 patients each, and then India race only one patient.

Based on the origin, most of the patients came from Sabah, 16 patients (44.4%), followed by 4 patients (11.2%) from Kedah, then each 3 patients from Selangor, Johor, Kuala Lumpur and Sarawak, 2 patients came from Perak and finally from Kelantan and Penang one patient each.

Table 1. Clinical characteristic of 36 patients with severe aplastic anemia

Age	
Range	1.8 – 15.7
Median	9.4
Sex	
Male	20 (55.6%)
Female	16 (44.4%)
Race	
Malay	13 (36.1%)
China	6 (16.6%)
India	1 (2.8%)
Dusun/Peribumi	12 (33.3%)
Iban	2 (5.6%)
Sino-kadazan	2 (5.6%)
Origin	
Sabah	16 (44.4%)
Sarawak	3 (8.3%)
Kedah	4 (11.2%)
Selangor	3 (8.3%)
Johor	3 (8.3%)
Kuala Lumpur	3 (8.3%)
Perak	2 (5.6%)
P.Pinang	1 (2.8%)
Kelantan	1 (2.8%)

Stem cell source was from the bone marrow in 19 patients (52.8%), peripheral blood stem cell (PBSC) in 3 patients (8.3%), combined of bone marrow and PBSC in 14 patients (38.9%).

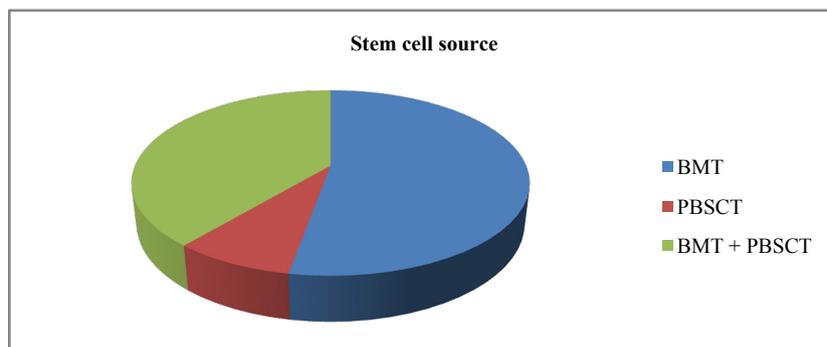


Figure 1. Stem cell source

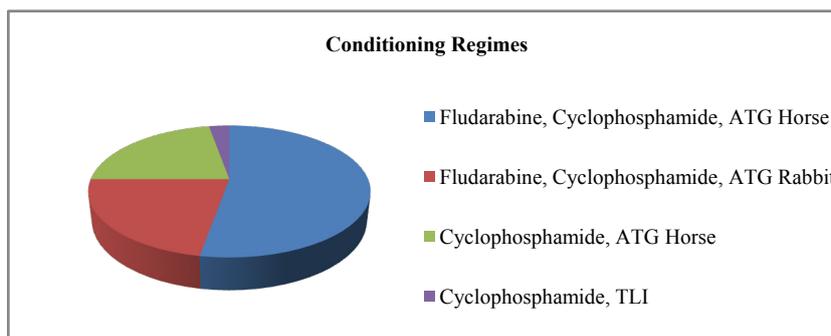


Figure 2. Conditioning regimes

The conditioning regimes used combination of fludarabine, cyclophosphamide and ATG horse in 19 patients (52.8%), combination of fludarabine, cyclophosphamide and ATG rabbit in 8 patients (22.2%), combination of cyclophosphamide and ATG horse in 8 patients (22.2%) and one patient (2.8%) used combination of cyclophosphamide and total lymphoid irradiation (TLI). (Figure 1)

The most important thing in patient who had undergo matched sibling stemcell transplantation was the time of engraftment, which was known by increase of granulocyte (ANC > 500 cells) and increase of platelet count more than 20,000/mm³ without transfusion of platelet before. In this report, we found the earliest day of granulocyte engraftment was 8 days after transplantation, and the longest was 24 days after transplantation. Most of the patient, 11 patients (29.7%) had granulocyte engraftment in 10 days after transplantation. Otherwise in platelet engraftment, we found the earliest day was 6 days after transplantation, and the longest was 31 days after transplantation. Most of the patients, 9 patients (24.4%) had platelet engraftment in 12 days after transplantation. But in order to platelet engraftment, there was one patient whose platelet count never reached 20,000/mm³ and this patient was finally classified into late graft rejection and need to do the second transplantation. (Figure 2)

Table 2. Days of granulocyte and platelet engraftment

ANC > 0.5	
Range	8 -24
Mostly	10 (11 patients – 30.6%)
ANC > 1.0	
Range	9-28
Mostly	11 (10 patients – 27.8%)
Platelet > 20.000	
Range	6- 28
Mostly	12 (9 patients – 25.0%)
Platelet > 50.000	
Range	8 – 73
Mostly	14 (7 patients – 19.4%)

The incidence of febrile neutropenia was common in patients with SAA, it is caused by the low patient's body mechanism to facilitate bacterial, fungal or viral to infected patients. The incidence of febrile neutropenia in patients with SAA who will do the transplantation can occur before or during the conditioning or after hematopoietic stemcell transplantation. In this report we found that 13 patients (36.1%) had episodic of febrile neutropenia before transplantation, 11 patients (30.6%) had febrile neutropenia after transplantation, then 8 patients (22.2%) had febrile neutropenia before and after transplantation while 4 patients (11.1%) never had episodic of febrile neutropenia before or after hematopoietic stemcell transplantation.

In this report we also had 4 patients (11.1%) suspected to have fungal infection, due to the long episodes of fever, who showed no improvement after being given antibiotics, but those patients had clinical improvement after being given antifungal. In this report we also found one patient (2.8%) suffering from viral infection, which was known by PCR CMV investigation that showed positive result 16 days after transplantation.

Another complication was VOD (veno occlusive disease), but in this report we found no patient who had VOD. Another complication that was important and need to be watched was the incidence of GvHD (graft versus host disease). We found 2 cases of GvHD after transplantation, one patient developed acute GvHD on the skin obtained on day 6 post transplantation (grade I), and increased to grade II on day 22, but managed to overcome by giving oral cyclosporin and prednisolone. Another case developed chronic GvHD in the mouth, that came after 100 days post transplantation, but managed to overcome with the provision of effective immunosupresant and corticosteroid.

Another complication was hemorrhagic cystitis with the clinical symptoms of microhematuria. This is caused by cyclosporin administration during conditioning phase. There were 6 patients (16.7%) who had symptoms of microhematuria.

Another complication was the effect to the vital organs due to cytotoxic drugs used at the conditioning phase or after post transplantation. There were 5 patients (13.9%) with hypertension, 4 patients (11.1%) had impaired renal function that was seen in increased creatinine level, 3 patients (8.3%) had impaired liver function that was seen in increased of liver enzyme, and one patient had impaired metabolic acidosis.

Another complication was the oral and gastrointestinal mucositis that resulted from the administration of cytotoxic drugs to the patients. There were 7 patients (19.4%) who suffered moderate mucositis that usually required TPN (total parenteral nutrition) for nutritional intake, another 18 patients (50.0%) only had mild mucositis and 11 patients (30.6%) had no mucositis during post transplantation period.

For the purpose of nutritional intake during post transplantation period, there were 11 patients (30.6%) required TPN administration, that varied between 3 – 14 days, while the remaining 25 patients (69.4%) did not require TPN.

Table 3. Complication after BMT

Febrile neutropenia	32 patients (88.9%)
Fungal Infection	4 patients (11.1%)
Viral infection	1 patient (2.8%)
Mucositis	
Mild	18 patients (50.0%)
Moderate	7 patients (19.4%)
VOD	nil
GvHD	
Acute GvHD	1 patient (2.8%)
Chronic GvHD	1 patient (2.8%)
Cystitis	6 patients (16.7%)
Toxicity	
Hypertension	5 patients (13.9%)
Renal	4 patients (11.1%)
Liver	3 patients (8.3%)
Metabolic acidosis	1 patient (2.8%)

The length of stay of SAA patients who were treated in the BMT ward ranged between 15-35 days after hematopoietic stemcell transplantation, with an average of 22.2 days stay. One important thing to know in SAA

patient is the history of previous blood transfusion administration. The more SAA patients received blood transfusion, the greater the possibility for the patient to get rejection after hematopoietic stemcell transplantation. We found 4 patients (11.1%) who had history of massive transfusion and received more than 200 units of blood components prior to hematopoietic stemcell transplantation.

Outcomes were obtained from hematopoietic stemcell transplantation at the BMT ward IPHKL for 10 years experience is very good. No patients died after hematopoietic stemcell transplantation, 34 patients were cured after a single transplantation and 2 patients had late graft rejection, but all were cured after a second hematopoietic stemcell transplantation 3-4 months later.

4. Discussion

Hematopoietic stemcell transplantation is the first choice in young patients with Severe Aplastic Anemia (SAA), who have HLA matched sibling donor, because in older patients, the risk of getting Graft versus Host Disease (GvHD) is higher and more severe than in younger patients. [1-6]

On review that conducted to SAA patients who had undergo allogenic hematopoietic stemcell transplantation in Bone Marrow Transplantation (BMT) ward in Institut Pediatrik Hospital Kuala Lumpur (IPHKL) during the last 10 years, there were 36 patients with SAA with age range between 1 year 8 months to 15 years 7 months, and the mean age was 9.4 years. From 37 patients, 20 (55.6%) were boys and 16 (44.4%) were girls. This was in accordance with some literatures that showed the incidence of SAA with nearly similar affects in boys and girls. [1,2,3]

Melayu race had the highest ranks of SAA patients (36.1%), because it was the majority race in Malaysia. But surprisingly there were considerable amount of the dusun/peribumi race (33.3%), which was a race in Sabah, this was in accordance with the origin of SAA patients, in which many of them came from Sabah and Sarawak region (52.8%). This showed that the referral system between hospitals in Malaysia has been well coordinated, because although different islands with IPHKL, did not affect the referral of patients who were indicated for allogenic hematopoietic stemcell transplantation.

From this review, for the source of stem cells, the most widely taken (52.8%) was bone marrow harvesting from the bone marrow donor, because it was the best source of hematopoietic stem cells and less risk for the onset of GvHD compared with Peripheral Blood Stem Cell (PBSC). [9,10] But another cases (38.9%) used the combination between bone marrow and PBSC as the source of stem cells. This was done by considering the number of stem cells in order to get that much, for faster onset of engraftment in transplantation recipients. [9,10] Although the risk for onset of GvHD was greater, but the administration of immunosuppressive drugs as prophylactic therapy to the onset of GvHD, such as Methotrexate and Cyclosporin, had proven to be effective to reduce the incidence of GvHD in patients with SAA post transplantation. [11]

Conditioning regimes for use in patients with SAA, mostly (75.0%) used a combination of fludarabine,

cyclophosphamide and anti thymocyt globulin (ATG). This was evidenced by the high number of engraftment in SAA patients taking this combination during conditioning, from the review for the last 10 years, there were only 2 patients (5.6%) who had graft rejection after transplantation, so this combination was still the main choice until now. [12,13,14]

The time span for engraftment of granulocyte, varies from 8 to 24 days, with an average of 13.2 days, and mostly begin to occur engraftment of granulocyte at day 10 post transplantation (30.6%). Whereas the time span for engraftment of platelets, varies between 6 to 31 days, with an average of 14.6 days, and mostly begin to occur engraftment of platelets at day 12 post transplantation (25.0%). There was an exception in 1 case, who never achieved platelet levels above 20.000, which means that the patient had late graft rejection and was indicated to undergo a second transplantation. From this review, with a high number of engraftment that occur in the first transplantation (94.4%), we found out the proper use of conditioning regimes prior to transplantation, also the availability of source of hematopoietic stem cell will affected the success of the onset engraftment in transplantation recipients. [12,13,14]

One of the unwanted complications in patients who had undergo hematopoietic stemcell transplantation was the onset of GvHD, the result of this review showed only 2 cases of GvHD (5.6%), 1 case of acute GvHD and one other case of chronic GvHD. This result demonstrated the utility of prophylactic medication against the possibility of GvHD at post transplantation care in BMT ward, such as the administration of Methotrexate on day 1,3,6 and 11 post transplantation as well as Cyclosporine, starting 1 day before transplant to 1 year after transplantation. To provide optimal results in the prevention of GvHD, the cyclosporine levels should be routinely monitored in the blood, so that we could adjust the dose until the optimal dose and steady as controlling the onset of GvHD. [4,5,11]

Another complication that often occur was the incidence of febrile neutropenia. Almost all patients (88.9%) had experienced episodes of febrile neutropenia, that occurred before or after bone marrow transplantation. This was due to the decreased number of granulocyte even to zero, in which granulocyte were useful as a defense mechanism against invading microorganisms from the outside. However the episodes of febrile neutropenia in patients with SAA, mostly experienced clinical improvement after being given the first line antibiotics (Cefepime/Tazocin + Amikacin), another patients improved after the replacement with second line antibiotics (Meropenem/Imipenem), and the remain (11.1%) experienced clinical improvement after being given anti fungal drug. [15,16]

Another complication that often occur was the incidence of mucositis of the mouth and gastro intestinal tract, resulting from the administration of cytotoxic drugs at the time of conditioning. There were 25 patients (69.4%) with mucositis that varies from mild to moderate, and 11 patients (30.6%) of them need to get Total Parenteral Nutrition (TPN) for nutritional intake. To minimize the incidence of mucositis, we carried out various actions, including giving nystatin and fluconazole during treatment, and doing good oral hygiene. [17]

The most important result of this review was about the outcomes from the patients, from 36 patients with SAA who underwent hematopoietic stemcell transplantation, all of them (100%) were still alive and recovered from aplastic anemia that previously suffered. Although there were exceptions on 2 patients who experienced late graft rejection in the first transplantation, but after the second transplantation in the next 3-4 months, the two patients were also cured from aplastic anemia. Potential causes of graft rejection in this case were due to a history of multiple transfusions prior to hematopoietic stemcell transplantation in one patient (received 40 unit of packed cells and 268 units of platelets). This was similar with some literatures which stated that a history of multiple transfusions was one of the most important factors for the onset of graft rejection in patients after hematopoietic stemcell transplantation. [18] The other one patient did not obtain multiple transfusion history, but a history of getting some traditional medicine for about 4-5 months before decided to return to medical treatment and agree to do the hematopoietic stemcell transplantation. However, this result was greater than some literatures that stated the survival rate of hematopoietic stemcell transplantation in patients with severe aplastic anemia ranged from 80-85%. [7,8,19]

Finally, the author concluded that the outcomes resulting in severe aplastic anemia patients after hematopoietic stemcell transplantation in IPHKL were very good, and the author hopes to be able to open a center for hematopoietic stemcell transplantation at the hospital where the author work, in order to save patients with aplastic anemia who had very poor prognosis, because of the ineffectiveness of immunosuppressive drugs and the absence of hematopoietic stemcell transplantation center, as the first choice therapy for patients with severe aplastic anemia.

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