Adult Allogeneic Haematopoietic Stem Cell Transplantation: A Single Centre Experience in Malaysia

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SUMMARY

We analysed the outcome of 104 patients from a single institution who underwent allogeneic haematopoietic stem cell transplantation (AHSCT) from their HLA-identical siblings between 1993 and 2006. Sixty-nine percent of patients had peripheral blood stem cell (PBSC) as the stem cell source and the remaining had bone marrow (BM). The majority of patients are Chinese (60%) followed by Malays (24%) and Indians (14%). The median time to reach white cell counts of >1x10^9/L and platelet counts of >30x10^9/L was 13 and 15 days, respectively in patients who had PBSC transplantation compared with 16 and 25 days in patients who had BM transplantation, (p<0.0001 and p<0.001). Acute graft-versus-host disease (aGVHD) of grade II to IV was observed in 34% of patients and chronic graft-versus-host disease (cGVHD) in 38% of patients. Although not statistically significant, there was a higher incidence of overall aGVHD in Indian patients (73%) compared to Chinese and Malays (57% and 56% respectively). There was no significant difference in the incidence of aGVHD and cGVHD with the source of stem cells. Overall survival (OS) and disease free survival (DFS) was 50% and 60% at five years respectively. Multivariate analysis showed that patients transplanted in standard risk and those who had limited cGVHD had a significant better OS, (p=0.05 and p=0.05). Patients who had cGVHD and transplanted in standard risk had a better DFS, (p=0.002 and p<0.001). In summary, AHSCT in standard risk patients is associated with a better outcome than those transplanted in high risk and although not statistically significant, there is a higher incidence of aGVHD in Indian patients.

KEY WORDS:
Allogeneic transplantation, Ethnicities, Graft-versus-host disease, Standard risk

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (AHSCT) has emerged as the standard therapy to treat a variety of hematological malignancies and disorders. Since its first accomplishment in human in 1957,[1] its use has rapidly expanded over the last decade with a broadened indication to include many other non-haematological disorders. Factors which determine the outcome of AHSCT have been quite well established. Age of donors and recipients, HLA status, disease status, cytomegalovirus (CMV) status are some of the factors which have been implicated in determining the overall survival of the recipients of AHSCT[2,3,4].

It is well reported that lower risk of graft versus host disease (GVHD) has been documented in homogenous populations e.g. in Japan and Scandinavian countries[5,6]. Other reports demonstrated that non-Caucasian populations have a higher incidence of acute GVHD (aGVHD) or chronic GVHD (cGVHD) and a higher transplant related mortality (TRM)[7,8,9]. The poor outcome was thought to be contributed partly by the general poor socio-economical status and lack of health care accessibility in these patients[8]. However, these can not entirely explain the findings especially now it has been reported that genetic polymorphism amongst the different ethnicities play a role in pharmacokinetics of certain drugs and perhaps in disease biology as well[10,11]. This may well partly explain the different outcome of AHSCT amongst the different racial populations.

There has been little research conducted in looking at the other ethnic groups in Asian countries. Malaysia is a multi-ethnic country with Malay, Chinese and Indian being the major racial groups. We started our first allogeneic bone marrow transplantation in the paediatric population in 1987 and adults in 1993. It is with this interest that we embarked on this study to report the transplant outcome of patients and to determine if ethnic disparity and other known factors play a role in the outcome of AHSCT in our institution.

MATERIALS AND METHODS

This was a retrospective study of all patients who were admitted to the adult haematology unit and underwent allogeneic bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) in one single centre between 1993 and 2006. All patients included in these studies had HLA-identical sibling donor cell transplantation. One patient who received an unrelated donor was not included in this study. Data was retrieved from the patients' case notes.

Patients were categorized by ethnic group; Malay, Chinese, Indians and others. Patient ethnicity was defined according to national identification documents. It is further defined by patient ancestral origin; Malay patients had an origin from Malaysia or Indonesia, Chinese from the China continent and Indians from Indian continent.

Other additional information analysed were age and gender of patients and donor, CMV status, disease status, type of disease, stem cell source, interval from diagnosis to

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transplantation, engraftment parameters and the number of blood products used. The infused cell dose pre-freezing including nucleated mononuclear cell for BMT, $CD34^+$ cells and $CD3^+$ cells for PBSCT were also recorded where available.

Disease status was classified into two major risk groups. Patient with standard risk group was defined as those who were transplanted in first complete remission (CR) and chronic phase in chronic myeloid leukemia (CML) patients. Patients with aplastic anaemia or myeloproliferative disease were also categorized as standard risk. Those transplanted beyond first CR are defined as high risk.

The majority of patients received busulphan and cyclophosphamide as their conditioning regimen prior to stem cell infusion. All patients received standard GVHD prophylaxis with cyclosporin and methotrexate. Diagnosis and clinical grading of aGVHD and cGVHD were documented by the attending physician according to established criteria[12]. Histological diagnosis for GVHD was obtained only when procedures were deemed appropriate by attending physicians. Engraftment parameters evaluated were time in days to the first of three consecutive days of white cell counts $>1x10^9/L$, and platelet count $\geq$ 30 $x10^9/L$. Non engraftment is defined when these two findings are not seen after day 99. Disease free survival (DFS) was calculated from the time of transplantation to relapse or death. Overall survival (OS) was calculated from time of transplantation to death or date of last follow up if appropriate.

Statistical analysis
Statistical analysis was performed using Statistical Analysis for the Social Sciences (SPSS) 13 for Windows. Fisher exact test, χ^2 test, independent T sample test and non-parametric test e.g. Mann-Whitney were used when appropriate. Survival curves were constructed using Kaplan-Meier curves and the variables were compared with log rank analysis and cox regression analysis. A *p value* of <0.05 was identified as significant.

RESULTS

A total of 104 patients were recruited in this study. Of these, 62 (60%) were Chinese, 25 (24%) Malays, 16 (14%) were Indians with only two were from other races. All patients received cyclosporine and methotrexate as GVHD prophylaxis. Underlying diseases for transplantation were mainly CML and acute myeloid leukemia (AML), followed by acute lymphoblastic leukemia (ALL) and aplastic anaemia (AA). Other underlying diseases were lymphoma (5), myelodysplastic syndrome (1), myelofibrosis (2) and myeloma (1). Patients and donor characteristics are depicted in Table I.

$CD3^+$ result was only available in 47(66%) patients who had PBSC infusion after year 2000. Three patients who had BMT did not have records of their nucleated mononuclear cell (NMC) dose. There were a total of 53 female donors but only 27 of them had records of parity.

Engraftment parameters
The engraftment parameters were evaluable in 102 patients. One patient died before engraftment and one had missing data. The median times to white cell and platelet engraftment in all patients were 13 days (range: 0-42 days) and 17 days (range: 0-99 days), respectively. In patients who had bone marrow (BM) as the source of stem cells, the median time to white cell and platelet recovery were 16 days (range :11-42 days) and 25 days (range:10- 100) days respectively. Patients who had peripheral blood stem cell (PBSC) infusion, the median time to white cell and platelet recovery were 13 days (0-18 days) and 15 days (0- 100 days) respectively. There was a significant reduction of days to white cell recovery and platelet recovery in PBSC compared to BM, $p<0.0001$ and $p<0.001$ respectively.

The total blood products used is showed in Table II.

Graft versus host disease
One hundred and three patients were evaluable for incidence of GVHD. Sixty-one patients (59%) had documented aGVHD and $\geq$grade 2 aGVHD was seen in 35 (34%) patients. Although there was an increase incidence of aGVHD in Indian patients, it was no significant. Thirty four (39%) patients of the total evaluable 88 patients had documented cGVHD and 38% (13) of these patients had extensive cGVHD. Again, there was no significant difference between the races. The risk of GVHD of the three races is showed in Table III.

There was no significant difference in the overall incidence of GVHD in those patients who had BM or PBSC as the stem cell source. Seventeen of the 32 patients (53%) who had BM infusions developed aGVHD, 41% of these (7 patients) had $\geq$ grade 2 aGVHD. In those patients who had PBSC infusion, 61% (43 patients) developed aGVHD, 65% (28) of them had $\geq$ grade 2 aGVHD. Chronic GVHD was seen in 32% (9) and 41% (24) of patients who had BMT and PBSCT respectively.

Age of patient and donor did not have any significant impact on the incidence of aGVHD(p=0.10 and 0.07 respectively). A history of preceding aGVHD is observed to have a higher incidence of cGVHD, p=0.007. Age of patient played a significant role in the incidence of cGVHD (p=0.04) where older age is associated with higher incidence of cGVHD. This is not observed in donor's age. (p=0.09)

The doses of $CD34^+$ cells, $CD3^+$ cells and NMC had also no significant impact in the GVHD risk. We found no significant association between sex mismatch, parity of donor and CMV status of patients/donors with incidence of GVHD.

Overall survival and disease free survival
The median follow up period for surviving patients were 1.75 years (range: 0.02-13.5 years). Forty nine patients died within the follow up period. The major causes of death are infection (41%) followed by underlying disease (35%) and GVHD (20%). In those evaluable patients for relapse, 30 of 93 (32%) patients relapsed.

The estimated OS at five years for all patients was 50%. (Figure 1) Factors affecting OS that were significant on univariate analysis were risk group, race, stage of cGVHD,

presence of aGVHD and severity of aGVHD. After a multivariate cox regression analysis, only stage of cGVHD and risk groups were identified to be significantly associated with OS (Table IV). The OS in standard risk patients were significant higher than those transplanted in high risk, 60% versus 30% at five years respectively, p= 0.009 (Figure 2).

The DFS at five years was 60%. There were only two factors which correlate well with DFS; risk group and presence of cGVHD. DFS was also more favourable in patients transplanted in standard risk than high risk (75% versus 40% at five years), p<0.0001 (RR 3.7, CI 1.77-7.7). (Figure 3) There was also a significant improvement in DFS in patients who have cGVHD than those who did not (80% versus 50% at five years), p=0.002 (RR 5.1, CI 1.78-14.7). No other factors were significant.

DISCUSSION

Malaysia has a multiracial population comprising of 65.1% Malay, 26% Chinese and 7.7% Indians[13]. The first BMT was performed in paediatric patient in 1987 followed by an adult patient in 1993. By the end of 2006, there have been more than 800 AHSCT performed. However, there have not been any published reports on our local transplantation activities except for two reports published more than a decade ago[14,15]. It is therefore important to study the heterogeneity of this population in determining any factors which may alter the outcome of patients.

In this study cohort, there were a relatively higher number of Chinese patients contributing to 60% of the total transplanted patients. This is probably due to the location of our hospital where the population is predominantly Chinese. There have been a few recent studies which indicated that ethnicity play a role in determining the transplant outcome including survival as well as GVHD risk[6-9]. It is reported that the non-Caucasians especially the blacks have a higher mortality rate as well as an increased aGVHD risk[9]. There has not been any convincing explanation for such a difference although differing socio-economical background is one of the postulated causes[8]. Genetic differences amongst races are increasingly being studied and it is well documented that different racial groups react differently to certain drugs[16,17]. Recent studies on gene polymorphism in the metabolism on warfarin had established the role of ethnicities which may provide further insights in other drugs and disease biology[11]. In this study, we found no significant difference in terms of OS and DFS between the three races. The overall incidence of severe aGVHD in this study was 34% and it is not surprisingly higher when compared to a more homogenous population e.g. Scandinavian population where the reported severe aGVHD is only 17%[6]. Although the incidence of overall aGVHD and ≥ grade 2 aGVHD appeared to be higher in Indian patients when compared with the other two major races, this was not significant. This may be due to the relative small number of Indian patients recruited in this study. However this finding should be further explored and postulation of genetic polymorphism in metabolism of drugs or disease biology may play a role in the increased risk of GVHD amongst Indian patients.

Consistent with the study by Karanth *et al* where the incidence of grade 2 or more aGVHD is higher in the non-Caucasians compared to the Caucasians (48% versus 26%), similar results were observed in this study[7]. In other studies in Asia, the overall incidence of aGVHD differed amongst countries, ranging from 21% to 62%[18-21]. This probably can be explained by the different ethnic groups as well as the possible different health care system available in each country.

PBSC has emerged as an alternative source of stem cell for AHSCT in the past decades due to the faster engraftment, lower need of transfusion and shorter hospital stay when compared with BMT[22-26]. The EBMT activity survey revealed that 65% of stem cell source for AHSCT is now peripheral blood derived[27]. We confirmed that there is a significant earlier recovery of white cell count and platelet count in PBSCT compared to BMT and were consistent with other published studies[23,25,28,29].

Table I: Patients and Donor Characteristics

Characteristics	
Median age (range) years	29 (13-47)
Sex (M:F)	56: 48
Race	
Malay	25 (24)
Chinese	62 (60)
Indian	15 (14)
Others	2 (2)
Disease	
AML	37 (35)
ALL	15 (14)
CML	34 (33)
AA	9 (9)
Others	9 (9)
Status	
First CR/CP	60 (58)
Beyond first CR/late CP	16 (15)
PR	4 (4)
Not in remission or CP	12 (11)
Pretransplantation Risk	
Standard	72 (69)
High	32 (31)
Conditioning	
Bu/Cy	81 (78)
Fludarabine based reduced intensity	23 (22)
Source of stem cells	
Bone Marrow	32 (31)
Peripheral Blood	71 (68)
Both	1 (1)
Infused cell dose (mean)	
NMC ($x10^8$/kg) (range)	2.4 (0.7-4.8)
CD34 ($x10^6$/kg)	3.3 (0.35-8.3)
CD3 ($x10^7$/kg)	15.3 (1.04-64)
Female donor to male recipient	22 (21)
CMV status (donor/recipient)	
+/+	76 (73)
+/-	8 (8)
-/+	2 (2)
-/-	1 (1)
unknown	17 (16)
Donor Sex (M:F)	51:53
Donor median age (range)years	28.5 (6-57)

Table II: Total blood products used

Blood products	BMT	PBSCT	P	Total
SDP median (range)	1 (0-12)	2 (0-63)	0.006*	1 (0-63)
RDP median (range)	42 (0-160)	15 (0-223)	0.03*	19.5 (0-223)
PC median (range)	4 (0-20)	4 (0-87)	NS	4 (0-87)

SDP, single donor platelets; RDP, random donor platelets; PC, packed cells

Table III: Incidence of GVHD amongst the three races

Race	aGVHD (%)	≥grade 2 aGVHD (%)	cGVHD (%)
Malays	14(56)	9 (36)	10 (45)
Chinese	35 (57)	17 (27)	19 (36)
Indian	11 (73)	8 (53)	5 (42)

Table IV: Analysis of various variables in determining overall survival

Variable	N (%)	P value		RR (95% CI)
		Univariate analysis	Multivariate analysis	
Age				
<30 years	62 (60)	0.41		
≥30 years	42 (40)			
Race				
Malays	25 (24)	0.017*	0.87	
Chinese	62 (60)			
Indians	15 (14)			
Others	2 (2)			
Indian	15 (14)	0.030*	0.778	
Non Indians	89 (86)			
Risk group				
Standard Risk	72 (69)	0.009*	0.049*	3.95
High Risk	32 (31)			(1.01-15.0)
Source				
BM	32 (31)	0.65		
PBSC	71 (69)			
Stage of cGVHD				
Limited	19	0.018*	0.049*	4.9
Extensive	13			(1.01-23.9)
cGVHD				
Yes	34 (39)	0.062		
No	54 (61)			
aGVHD				
Yes	42 (41)	0.003*	0.14	
1	26 (25)			
≥2	35 (34)			
aGVHD				
Yes	61 (59)	0.037*	0.98	
No	42 (41)			

Besinger *et al* reported a higher requirement for red cell and platelet transfusion in BMT than PBSCT[24]. Similar findings were noted in study by Ustunn *et al*. although it was not statistically significant[30]. In this study, we found that there is no difference in the red cell transfusion between the two groups but there is a significant increase in random donor platelet (RDP) requirement in the BMT patients than the PBSCT patients. On the contrary, the need for single donor platelet (SDP) transfusion is higher in PBSCT patients. This contradictory result may be because SDP has only widely been available in the recent years.

It was observed that there was an increase in incidence of aGVHD and cGVHD in patients who had PBSC as their source of stem cell transplantation[25,31]. However, we found no significant increase in the incidence of aGVHD and cGVHD in patients who had PBSCT compared with those who had BMT and this is consistent with findings from other studies[23,29,30].

Many other factors which have been identified to affect the risk for aGVHD are the degree of histocompatibility, age of patients and donors, sex mismatch and parity of donors[32-36]. However, we do not find any correlations between age, parity and CMV status of patient and donor with the incidence of aGVHD although cGVHD risk was observed to be higher in older patients and in patients who had preceding history of aGVHD and this is consistent with other published studies[37-39]. The available data for the parity of donors are few and the majority of the patients and donors in this study are CMV seropositive and hence the findings should be further explored.

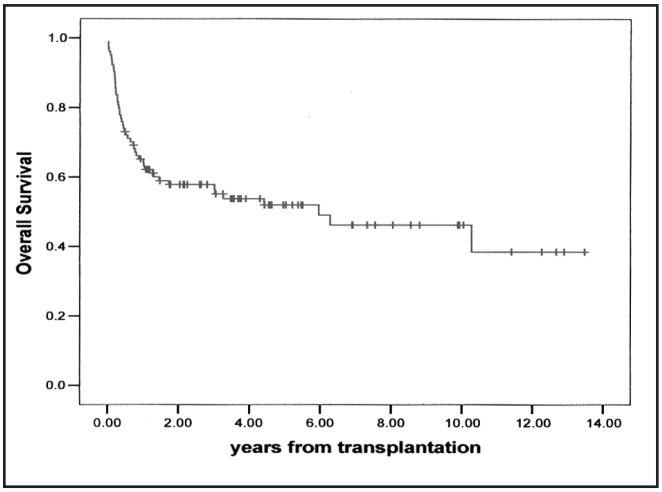

Fig. 1: Overall Survival of all patients

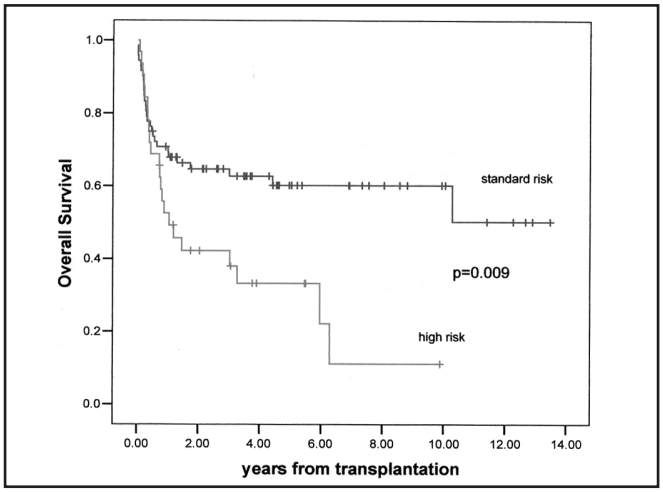

Fig. 2: Overall Survival between risk groups

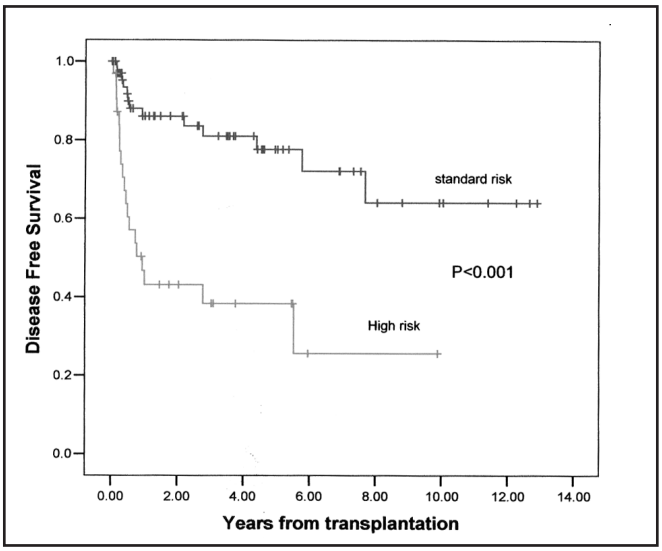

Fig. 3: Disease Free Survival between different risk groups

Numerous studies have examined, in a variety of settings, the relationship between clinical outcomes and total graft doses as well as doses of individual cell subpopulation. There was no significant correlation between the incidence of GVHD and the total number of $CD34^+$ cells and NMC found in this study which is in keeping with other studies[34,40,41].

GVHD is thought to be caused by the donor T cells reacting to the host cells and involved activation of a number of cytokines and other yet unknown mechanisms. The importance of $CD3^+$ cells for the development of aGVHD and cGVHD has been reported previously[37, 42]. In this study, we attempt to establish if $CD3^+$ cell dose has a role in determining the incidence of GVHD in our patients. We found no significant correlation with $CD3^+$ cell dose with the incidence of aGVHD as well as cGVHD. This was consistent with previous studies[24, 40]. The relative lack of severe GVHD despite the high numbers of lymphocytes infused into these patients had been attributed to a reduction in function of T cell and NK cells in granulocyte colony-stimulating factor (G-CSF) treated normal donors[43]. Another possible explanation is that unmanipulated G-CSF mobilized PBSC already contain T-cell doses in excess of the minimal threshold required for initiating responses leading to aGVHD. Kernan *et al* suggested that the critical donor T-cell dose may be as low as $1x10^5$/kg of patient weight; T- cell dose higher than this does not necessarily lead to greater occurrences of aGVHD[44].

The major cause of death is infection and underlying disease which is consistent with many other studies. The significant factors identified in this study which affect the survival were the disease status at transplantation and the severity of cGVHD.

Patients with no cGVHD had a higher incidence of relapse. It is not surprising that patients who were transplanted at a later stage or beyond first CR, the prognosis is worse[8,20,21]. However, it is interesting that patient with limited cGVHD had a significantly better OS and only patients with cGVHD had a longer DFS.

It is known that cGVHD is associated with reduced rate of relapse and this is thought to be due to the graft versus leukemia effect[45, 46]. In extensive cGVHD, it is possible that patients may require long term and stronger immunosuppressive therapy which may in turn increase the risk of infection and perhaps mortality. This is better explained in the study by Lee *et al* [47]. Similar findings were also observed by Gratwohl *et al* although the patient population studied is limited to CML patients[48].

In conclusion, we found no difference in OS and DFS in either PBSCT or BMT. Patients who were transplanted at a later stage or beyond first CR had a poorer prognosis. In this study, we found no difference in the outcome of transplantation and ethnicities although Indians seemed to have a higher incidence of GVHD. A further study will be required to explore the relationship of ethnicities and transplant outcome.

The limitation of this study are the number of patients included is small especially the Indian patients and it is a retrospective study where not all data were available for analysis.

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