Viva-Asia Blood and Marrow Transplantation Groups – A Survey of Consortium Activity over a 12-year Period (2000 to 2011)

Dear Editor,

Haematopoietic stem cell transplantation (HSCT) is an established treatment for many malignant and non-malignant childhood conditions. Because of regional differences in disease spectrum and donor availability, transplant approaches may vary. The Viva-Asia Blood and Marrow Transplantation (VABMT) Group was established in 2009 to address the specific transplant issues for children that were represented in the transplant centres in the East. Members of this working group perform paediatric HSCTs in 6 Asia Pacific countries, including 3 centres in Singapore, 2 in Hong Kong, 2 in mainland China, 2 in Thailand and 1 each in Malaysia and Philippines.

The volume of HSCT and the trends of transplant care, data on transplantations performed from 2000 to 2011 inclusive were obtained from all 11 centres. Analyses focused on the types of disease, donor, stem cell source, and changes of practice over time. The centres involved were from Singapore (KK Women's and Children's Hospital, National University Hospital, Mount Elizabeth Hospital), Hong Kong (Queen Mary Hospital, Prince of Wales Hospital), mainland China (Shanghai Children's Medical Centre, Nanfang Hospital), Thailand (Ramathibodi Hospital, Siriraj Hospital), Malaysia (Sime Darby Medical Centre) and Philippines (St Luke's Medical Centre).

All 11 centres performed both autologous and allogeneic HSCT. In the 12 years from 2000 to 2011 inclusive, there were a total of 1790 HSCTs performed: 1407 (78.6%) were allogeneic and the remaining 383 (21.4%) were autologous (Table 1). Among the allogeneic HSCTs, 54.9% were for non-malignant conditions and 45.1% for malignant diseases (Table 2). The proportion of HSCTs that were allogeneic increased from 75% in the first 6 years (early cohort) to 80.6% in the second 6 years (recent cohort) (Table 1).

All centres carried out allogeneic HSCTs for both malignant and non-malignant conditions. Overall, there were more transplants performed for non-malignant conditions (54.9%) compared to malignant conditions (45.1%). Acute myeloid leukaemia (AML)/myelodysplastic syndrome (MDS) (40.9%) formed the majority of allogeneic HSCT in malignant conditions (Table 2), followed by acute lymphoblastic leukaemia (ALL) (39.4%), chronic myeloid leukaemia (CML) (12.5%) and others (7.2%). For non-malignant conditions, more than half of the allogeneic HSCT were performed for haemoglobinopathy (62.7%), followed by severe aplastic anaemia (SAA) (17.9%), primary immune deficiency (8.4%), inherited metabolic disease (4.4%) and congenital bone marrow failure (4%).

Unrelated and related donors were almost equally used (Table 3): 48% were unrelated and 52% were related (40.8% were matched sibling/twin and 11.2% were haploidentical). This is consistent with the findings of the Europe Bone Marrow Transplant (EBMT) activity survey[1] in year 2010: unrelated source of stem cells was 53% compared with 41% in related human leukocyte antigen (HLA)-matched sibling source. Unrelated cord blood (CB) and haploidentical donor transplants were increasingly being performed in recent years for patients without a sibling or a matched unrelated donor (Table 3).

For matched-related source of stem cells, the majority (58%) were from bone marrow (BM), while peripheral blood stem cell (PBSC) formed 29.6% of the stem cells source (Table 4). Related CB formed a small percentage (4.4%). For unrelated source of stem cells, 71.1% were from BM or PB while 28.9% were from CB. Notably, the frequency of CB HSCT varied substantially among the 10 centres. For example in Singapore, KK Women's and Children's Hospital and Mt Elizabeth Hospital, and in Hong Kong

Table 1. The Total Number of Allogeneic and Autologous HSCT Performed from 2000 to 2011 among the Asian Centres

	Total	Year		*P* Value	Type of Conditions		*P* Value
		2000 – 2005	2006 – 2011		Malignant	Non-malignant	
Allogeneic HSCT	1407 (78.6%)	475 (75.0%)	932 (80.6%)	0.008	634 (63.5%)	773 (97.7%)	<0.001
Autologous HSCT	383 (21.4%)	158 (25.0%)	225 (19.4%)		365 (36.5%)	18 (2.3%)	
Total	1790 (100%)	633 (100%)	1157 (100%)		999 (100%)	791 (100%)	

HSCT: Haematopoietic stem cell transplantation

Table 2. The Absolute Number of Allogeneic HSCT Performed for Different Malignant and Non-Malignant Conditions

Disease	Total, n (%)	2000 – 2005	2006 – 2011	*P* Value
Malignant	634 (45.1%)	233 (49.1%)	401 (43.0%)	0.036
Non-malignant	773 (54.9%)	242 (50.9%)	531 (57.0%)	
Malignant disease				
Acute myeloid leukaemia	206 (32.5%)	78 (33.5%)	128 (31.4%)	0.008
Acute lymphoblastic leukaemia	250 (39.4%)	101 (43.3%)	149 (36.9%)	
Chronic myeloid leukaemia	79 (12.5%)	35 (15.0%)	44 (11.4%)	
Myelodysplastic syndrome	53 (8.4%)	9 (3.9%)	44 (11.9%)	
Other leukaemia	14 (2.2%)	3 (1.3%)	11 (2.4%)	
Lymphoma	22 (3.5%)	4 (1.7%)	18 (4.6%)	
Solid tumour	10 (1.5%)	3 (1.3%)	7 (1.4%)	
Non-malignant				
Severe anaplastic anaemia	138 (17.9%)	34 (14.0%)	104 (19.6%)	0.74
Paroxysmal nocturnal hemoglobinuria	2 (0.3%)	1 (0.4%)	1 (0.2%)	
Congenital bone marrow failure	31 (4.0%)	13 (5.4%)	18 (3.4%)	
Haemoglobinopathy	485 (62.7%)	155 (64.1%)	330 (62.2%)	
Epstein-Barr virus-related disease	1 (0.1%)	0	1 (0.2%)	
Hemophagocytic lymphohistiocytosis	9 (1.2%)	3 (1.2%)	6 (1.1%)	
Langerhans cell histiocytosis	1 (0.1%)	0	1 (0.2%)	
Autoimmune disease	1 (0.1%)	0	1 (0.2%)	
Metabolic disease	34 (4.4%)	11 (4.6%)	23 (4.4%)	
Primary immune deficiency	65 (8.4%)	23 (9.5%)	42 (7.9%)	
Others	6 (0.8%)	2 (0.8%)	4 (0.8%)	

Prince of Wales Hospital, unrelated CB formed 60 to 80% of unrelated stem cells sources (Table 5). Autologous HSCT accounted for 383 out of 1790 (21.4%) of total number of HSCT. Of these, 93.7% of autologous source of stem cells were peripheral blood stem cell and BM transplants.

Clinical application of allogeneic HSCT has been increasing steadily over the past 12 years as the number of unrelated BM/peripheral blood donors and CB units have become more readily available for public use. The number of allogeneic HSCT has increased significantly by more than 2 folds in our recent cohort than in the earlier cohort (Table 1). In the recent cohort, we found an increase in number of HSCT for non-malignant condition in almost all categories (Table 2). For SAA and haemaglobinopathy, the 2 most common types of non-malignant conditions, the number of HSCT had risen significantly from 34 to 104 cases for SAA and from 155 to 330 cases for haemoglobinopathy comparing the 2 cohorts.

Over the period, there was a significant change in donor source for allogeneic HSCT (Table 3). In the earlier period (2000 to 2005), 51.6% of allogeneic HSCTs were matched sibling/twin donor while unrelated adult donor/CB formed 36.8% of allogeneic HSCTs. In the recent period, unrelated adult donor/CB accounted for 53.6% of allogeneic HSCTs. This was made possible with the expansion of national and international marrow registries and public CB banks. Unrelated adult donor HSCTs increased from 119 to 361 while unrelated cord from 56 to 139 (P <0.001). The

Table 3. The Donor Sources for Allogeneic HSCT

Year	Total	Related 732 (52%)		Unrelated 675 (48%)		*P* Value
		Matched Sibling/Twin	Haplo-identical	Adult Donor	Cord Blood	
2000 – 2005	475	245 (51.6%)	55 (11.6%)	119 (25.0%)	56 (11.8%)	<0.001
2006 – 2011	932	329 (35.3%)	103 (11.1%)	361 (38.7%)	139 (14.9%)	
Total	1407	574 (40.8%)	158 (11.2%)	480 (34.1%)	195 (13.9%)	

Table 4. The Sources of Stem Cells from Matched-Related or Unrelated Donor

	Total, n (%)	2000 – 2005	2006 – 2011	*P* Value
MSD/Twin				
Bone Marrow	333 (58.0%)	143 (58.4%)	190 (57.8%)	<0.001
Peripheral Blood	170 (29.6%)	76 (31.0%)	94 (28.6%)	
Cord Blood	25 (4.4%)	17 (6.9%)	8 (2.4%)	
Others (combination)	46 (8.0%)	9 (3.7%)	37 (11.2%)	
Total	574 (100%)	245 (100%)	329 (100%)	
Unrelated Donor				
BM	181 (26.8%)	81 (46.3%)	100 (20.0%)	<0.001
PB	299 (44.3%)	38 (21.7%)	261 (52.2%)	
CB	195 (28.9%)	56 (32.0%)	139 (27.8%)	
Total	675 (100%)	175 (100%)	500 (100%)	

unrelated cord forms a small but significant source of unrelated stem cells from 11.8% to 14.9% over 2 periods among the Asia Pacific HSCT centres.

In matched-related donor HSCT, peripheral blood stem cell is a good alternative source, especially if there is a considerable discrepancy in body weight between the donor and recipient. The majority source of stem cells (58%) was from BM in a related setting. For unrelated adult donor, the source was usually peripheral blood which formed 44.3%. We saw a change in the proportion of peripheral blood from 21.7% to 52.2% (P <0.001) during the period of 2006 to 2011 inclusive. Related CB represented a small percentage but constituted an important source of stem cells, as the medical condition of the recipient may not allow time for the donor to grow up to be a marrow or peripheral blood stem cells donor.

In Japan, 60% of unrelated source of stem cells were from BM/PB and 40% were from CB.[2] Unrelated donors in Asia were relatively difficult to find because ethnic Asians are under-represented in most major international registries such as National Marrow Donor Program (NMDP) in the United States.[3] In recent years, The China Marrow Donor Program, with about1 million potential donors, opened its doors to international usage in 2012.[4] Before that, Asian Oriental recipients, especially ethnic Chinese, had to depend mainly on Buddhist Tzu Chi Stem Cell Centre in Taiwan. It was established in 1994 and has been one of the largest source of unrelated stem cells for Oriental recipients.[5]

Thirty-nine percent of unrelated HSCT were from CB (Table 3), a growing source of stem cells in this part of world with multiracial and multiethnic populations, especially in countries like Malaysia and Singapore. In the Asia Pacific

Table 5. The Sources of Stem Cells for Unrelated HSCT from Different Centres

Centres	Peripheral Blood/Bone Marrow	Cord	Total
China: Nanfang	150	4	154
China: Shanghai Children Medical Centre	136	30	166
Hong Kong: Prince of Wales Hospital	35	55	90
Hong Kong: Queen Mary Hospital	39	35	74
Malaysia: Sime Darby Medical Centre	11	10	21
Philippines: St. Luke Medical Centre	1	1	2
Singapore: Women's and Children's Hospital	8	27	35
Singapore: National University Hospital	37	23	60
Singapore: Mt. Elizabeth Hospital	3	7	10
Thailand: Siriraj	15	0	15
Thailand: Ramathibodi Hospital Mahidol University	45	3	48
Total	480 (71.1%)	195 (28.9%)	675

Bone Marrow Transplant (APBMT) survey in 2008, unrelated CB contributed 30 to 80% of unrelated HSCT in several centres, both for children and adult unrelated HSCT (unpublished data: Lila M, Atsuta Y, Hyo R, et al. APBMT annual report. Monograph 2010; v4).

In conclusion, the Viva-Asia HSCT Consortium gives us the opportunity to understand the different pattern of HSCT in Asia in terms of types of HSCT, choice of stem cells and indications for HSCT. Some of these patterns are unique to Asia. Continuing collaboration among centres in Asia will allow us to improve the outcomes of allogeneic HSCT for different diseases, as surveys form the backbone and pave the way for further collaborative studies and researches. In conclusion, the limitation of this study is that not all paediatric centres of the mentioned countries were surveyed.

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REFERENCES

1. Passweg JR, Baldomero H, Gratwohl A, Bregni M, Cesaro S, Dreger P, et al. The EBMT activity survey: 1990-2010. Bone Marrow Transplant 2012;47:906-23.
2. Kodera Y. The Japan Marrow Donor Program, the Japan Cord Blood Bank Network and the Asia Blood and Marrow Transplant Registry. Bone Marrow Transplant 2008; 42 Supp 1:S6.
3. Confer D, Robinett P. The US National Marrow Donor Program role in unrelated donor hematopoietic cell transplantation. Bone Marrow Transplant 2008;42 Supp1: S3-5.
4. Lu DP. Blood and marrow transplantation in mainland China. Hong Kong Med J 2009;15(3 Suppl 3):9-12.
5. Chen PM, Hsiao LT, Tang JL, Yen CC, Liu JH, Lin KH, et al. Haematopoietic stem cell transplantation in Taiwan: past, present and future. Hong Kong Med J 2009;15(3 Suppl 3):13-6.

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