SCIENTIFIC PAPER

Haematopoietic stem cell transplantation in Hong Kong

Albert KW Lie 李國維
WY Au 區永仁
Raymond Liang 梁憲孫

The first case of haematopoietic stem cell transplant (HSCT) was performed at the Bone Marrow Transplant Center, Queen Mary Hospital (QMH) in 1990. Since then three more transplant centres have been established: Prince of Wales Hospital (1991) mainly in paediatric transplant, Queen Elizabeth Hospital (1995) and Tuen Mun Hospital (2006) in adult autologous transplant. Up to the end of 2008, a little over 2000 transplants have been performed in Hong Kong, and QMH takes up about 85% of the total number of cases. A unified HSCT registry in Hong Kong is desirable and is yet to be established. At QMH, by the end of 2008, a total of 1708 transplant procedures have been performed with 83% (1417) being first-time transplants and the rest (291, 17%) are repeat transplants mostly for relapsed patients. The numbers of male and female patients are 955 and 753, respectively. The median age is 35.4 years (range, 3 months to 67 years) with 85.8% of the transplants performed in adults (>18 years). The type of donor includes 34% autologous, 1% syngeneic, 38% related allogeneic and 27% unrelated allogeneic. The top five indications of the first-time transplants are acute myeloid leukaemia (25.8%), chronic myeloid leukaemia (15.9%), lymphoma (14.6%), acute lymphoblastic leukaemia (14.5%), and myeloma (8.6%). With the development of peripheral blood stem cell collection, in recent years it is performed in 50% of the allogeneic and 80% of the autologous cases. Bone marrow harvest in autologous cases is only for patients who fail peripheral blood stem cell mobilisation. Transplant outcomes are reported to the Center for International Blood and Marrow Transplant Research and long-term survivals are in general comparable to international standard.

Introduction

In Hong Kong, the first case of haematopoietic stem cell transplant (HSCT) was performed at the Bone Marrow Transplant Center, Queen Mary Hospital (QMH) in May 1990 for a female patient with acute myeloblastic leukaemia (AML) with human leukocyte antigen (HLA)–matched sibling donor.[1] Since then three more transplant centres have been established, including Prince of Wales Hospital (PWH) in 1991, Queen Elizabeth Hospital in 1995, and Tuen Mun Hospital in 2006. Paediatric HSCT, both autologous and allogeneic, is performed at QMH and PWH. For adult patients, autologous HSCT is performed at all four hospitals while QMH is the only centre for allogeneic HSCT in adults. Unfortunately, a central registry of all HSCT activities is yet to be established in Hong Kong. Such a central registry is desirable not only for monitoring HSCT activities, but also for gathering information on long-term survival, late complications, uncommon conditions as well as changes in trends over the years which will help in planning the HSCT service for the future. Unofficial estimates of about 170 HSCTs are performed annually and a total of a little over 2000 HSCTs have been performed up to the end of 2008. Among the latter, 1708 (approximately 85%) were performed at QMH at a rate of about 130 per annum.

Haematopoietic stem cell transplant at Queen Mary Hospital

Among the 1708 HSCTs performed in QMH, 1417 (83%) were first-time transplants and the rest (291, 17%) were repeat transplants most commonly for disease relapse, less often for graft failure or secondary haematological malignancy (Fig 1). There was a slight male predominance among the patients (male 56%, female 44%). The median age at transplant was 35.4 years (range, 3 months to 67 years) [Fig 2] with 14.2% of the transplants performed in children and adolescent (ie <18 years), and the remaining 85.8% in adults.

Starting with bone marrow transplant (BMT) only in 1990, the first case of peripheral blood stem cell transplant (PBSCT) was performed for a female patient with relapsed non-Hodgkin's lymphoma (NHL) in 1992. Over the years, the annual number of PBSCT has overtaken BMT. In recent years, while the use of PBSCT is roughly equal to that of BMT in allogeneic transplant, it is almost 4 times that of BMT in autologous transplant. Bone

Key words
Hong Kong; Stem cell transplantation

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University Department of Medicine, Queen Mary Hospital, University of Hong Kong, Pokfulam Road, Hong Kong
AKW Lie, WY Au, R Liang

Correspondence to: Dr AKW Lie
Tel: 852 28553975
Fax: 852 28726896
E-mail: akwlie@hkucc.hku.hk

香港血液幹細胞移植概況

香港首宗血液幹細胞移植，於1990年在瑪麗醫院的骨髓移植中心進行。此後，威爾斯親王醫院於1991年開展兒童骨髓移植，而伊利沙伯醫院及屯門醫院亦於1995及2006年開展成人自體移植。截至2008年底，全港共已進行稍多於二千宗移植治療，而瑪麗醫院佔其中大約85%。目前香港仍有待發展出一個全港的血液幹細胞移植檔案庫。截至2008年底，瑪麗醫院已進行1708宗移植。其中83%（1417）為病者首次移植，其餘17%（291）主要因復發而重做。男女人數為955和753。中位年齡為35.4歲（由3個月至67歲），其中85.8%為18歲以上成人。供者分別為：34%自體、1%同基因、38%親屬異體及27%非親屬。首五項病症為：25.8%急粒、15.9%慢粒、14.6%淋巴瘤、14.5%急淋及8.6%骨髓瘤。隨著外周血幹細胞之普及，近年本中心有50%之異體及80%之自體移植皆應用此法。四份一之自體移植仍因採集外周血遇困難而用骨髓。本中心之所有移植後之跟進資料皆提供及CIBMTR，而長遠的存活數據大至興國際水平相約。

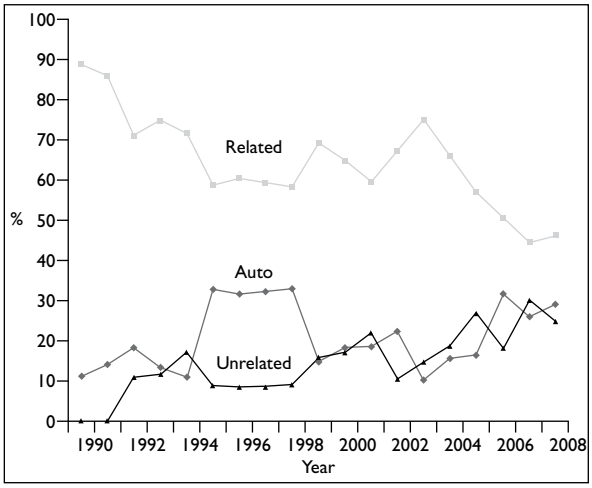

FIG 3. Donor relationship

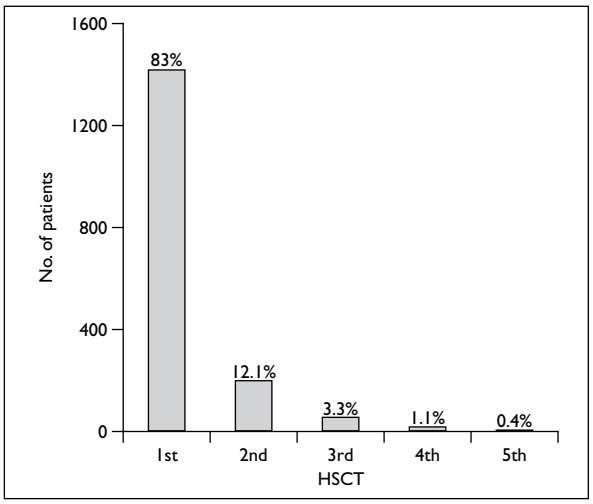

FIG 1. Number of attempts with haematopoietic stem cell transplant (HSCT) received by patients at Queen Mary Hospital
Total HSCT: 1708; 1st HSCT: 1417; 2nd or more HSCT: 291

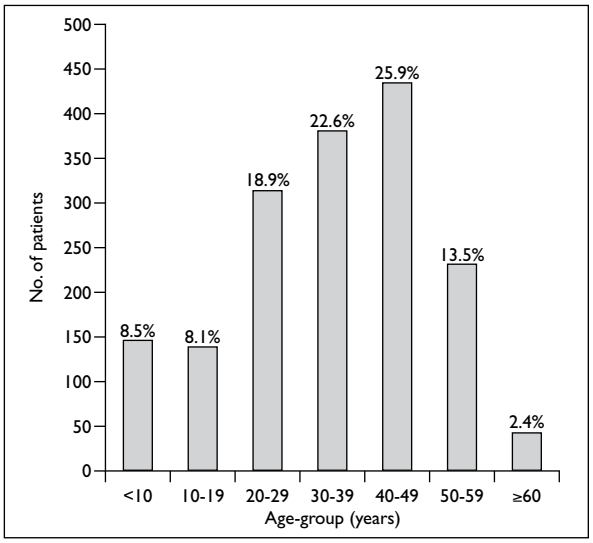

FIG 2. Patients' age at haematopoietic stem cell transplantation

marrow harvest is basically reserved for patients in whom PBSC harvest has failed or is expected to have poor yield due to extensive prior chemotherapy and/or radiotherapy. Hence, to ensure patients can benefit from the earlier engraftment with autologous PBSCT, timely consideration and early referral is of key importance.

Cord blood transplant (CBT) was first performed in 1994 for a 3-year-old girl with beta thalassaemia major using stem cells from an HLA-matched sibling, and unrelated CBT was first performed in 1998 for a 9-year-old boy with acute lymphoblastic leukaemia (ALL). Up to the end of 2008, a total of 31 CBTs have been performed mainly in paediatric and adolescent patients, and only four CBTs in adults.

The types of donor among the 1708 HSCTs include autologous (34%), syngeneic (1%), siblings (35%), other related donors (3%) and unrelated donors (27%). There is a trend with increasing proportion of autologous and unrelated HSCTs compared to related donations (Fig 3).

Among the paediatric patients, besides haematological malignancies, beta thalassaemia major,[2] congenital immunodeficiency syndromes[3] (eg severe combine immunodeficiency syndrome and Wiskott-Aldrich syndrome), paediatric solid tumours (eg neuroblastoma, rhabdomyosarcoma and medulloblastoma) and other congenital diseases (eg Diamond-Blackfan anaemia, Fanconi anaemia, dyskeratosis congenital and infantile osteopetrosis) make up a small but important fraction of curable patients (Table 1). For adults, the top five indications of the first-time transplants are AML (25.8%), chronic myeloid leukaemia (CML) (15.9%), NHL (14.6%), ALL (14.5%) and multiple myeloma (MM) (8.6%). In subsequent discussion, we shall focus on these five conditions, which make up approximately three

TABLE 1. Indications for haematopoietic stem cell transplant

Indication	%
Acute myeloblastic leukaemia	25.8
Chronic myeloid leukaemia	15.9
Non-Hodgkin's lymphoma	14.6
Acute lymphoblastic leukaemia	14.5
Multiple myeloma	8.6
Myelodysplastic syndrome	5.8
Paediatric solid tumours	2.6
Beta thalassaemia major	2.5
Severe aplastic anaemia	2.3
Adult solid tumours	1.8
Hodgkin's lymphoma	1.7
Immunodeficiency syndrome	1.6
Other congenital diseases	1.4
Acute biphenotypic leukaemia	1.1

TABLE 2. WHO classification of non-Hodgkin's lymphoma with allogeneic haematopoietic stem cell transplant

Histological diagnosis	No. of patients (n=73)
Diffuse large B cell	28
Lymphoblastic	12
Mantle cell	8
T/NK nasal-type cell	6
Peripheral T cell (NOS)	5
Burkitt's lymphoma	5
Follicular	4
Anaplastic large T cell	2
Angioimmunoblastic T cell	1
Maltoma	1
Marginal zone B cell	1

quarters of all HSCTs at QMH. The numbers of HSCTs for all five conditions are on an increasing trend over the years, except CML where there is a marked decrease since 2005 when imatinib became available for all such patients under the safety net scheme of the Hospital Authority. The increase in HSCT is particularly marked with MM in recent years, largely as a result of improved disease control with newer agents, such as bortezomib and thalidomide.[4,5]

Acute myeloid leukaemia

Of 231 patients—116 were in first complete remission (CR1), 58 in second complete remission (CR2), and 57 not in remission (NR)—having HLA-matched sibling HSCT, the respective overall survival (OS) at 5 and 10 years were 56.9% and 55.6% with CR1, 48.6% and 45.9% with CR2, and 18.2% and 15.6% with NR (Table 3).

For 59 HLA-matched unrelated HSCT (28 in CR1, 21 in CR2, and 10 in NR), the 5-year OS were 68.0% with CR1, 37.8% with CR2, and 25.9% with NR. The usual conditioning regimen is busulphan (Bu) 16 mg/m^2 over 4 days plus cyclophosphamide (Cy) 120 mg/kg over 2 days in HLA-matched sibling HSCT,[6] while for unrelated HSCT the Cy is increased to 150 mg/kg over 3 days.

Chronic myeloid leukaemia

Chronic myeloid leukaemia used to make up about a quarter of all the HSCTs annually and the conditioning regimen is Bu-Cy as in AML. With the introduction of imatinib, it has dropped to less than 5% in recent years. With 185 HLA-matched sibling HSCT, the 10-year disease-free survival (DFS) with chronic phase (CP, n=140), accelerated phase (AP, n=37) and blastic crisis (BC, n=8) were 53.0%, 25.0% and 0.0%, respectively. However, having effective salvage therapy in relapsed cases, such as termination of immunosuppression or donor leukocyte infusion in the past, and more recently with imatinib treatment, 10-year OS can still be maintained at 76.6% for CP and 25.7% for AP patients.

Only a small number of CML patients received unrelated HSCT (24 CP, 17 AP, and 6 BC; total=47), the 10-year OS are much the same for the different stages (52.6% for CP, 50.0% for AP, and 41.7% for BC).

Non-Hodgkin's lymphoma

A total of 148 patients received autologous HSCT with 24 in CR1, 65 in partial remission, 39 in CR2, and 20 in NR. The 10-year OS for the first three groups were 82.1%, 60.4% and 53.4%, respectively, while NR patients had very poor OS.

Allogeneic HSCT was performed for 73 patients of whom 63 were related donors (61 siblings, 2 others) and 10 were unrelated. Sixty-one patients had stage-IV disease at presentation and received direct allogeneic HSCT after initial disease control. The remaining 12 patients relapsed after initial autologous HSCT and then received second-time allogeneic HSCT as salvage. The histological diagnoses are as listed in Table 2. The conditioning regimen were Cy (120 mg/kg over 2 days) and total body irradiation (TBI; 12 Gy in 6 fractions over 3 days) in 47 patients, CBV[7] (carmustine 100 mg/m^2 daily day 1 to 3, etoposide 400 mg/m^2 every 12 hours from day 1 to 3, Cy 1800 mg/m^2 daily day 4 to 7) in 19, and other myeloablative regimens in 7. The 5-year OS was 57.5% in the direct allogeneic HSCT group and 45.7% with the second-time allogeneic HSCT group, showing no statistically significant difference between the two groups (P=0.447).

TABLE 3. Survival data of the top five adult conditions transplanted at Queen Mary Hospital*

Disease	Type of HSCT†	Stage	No. of patients	5-Year		10-Year	
				DFS (%)	OS (%)	DFS (%)	OS (%)
AML	Sib	CR1	116	50.3	56.9	47.3	55.6
		CR2	58	43.2	48.9	40.5	45.9
		NR	57	12.3	18.2	12.3	15.6
AML	Unrelated	CR1	28	52.5	68.0	-	-
		CR2	21	37.8	37.8	-	-
		NR	10	25.9	25.9	-	-
ALL	Sib	CR1	77	44.0	47.0	43.8	43.8
		CR2	27	18.3	26.2	18.3	21.0
		NR	9	0	16.7	-	-
ALL	Unrelated	CR1	27	57.1	57.9	-	-
		CR2	7	35.7	42.9	35.7	42.9
		NR	1	0	0	0	0
CML	Sib	CP	140	61.4	81.3	53.0	76.6
		AP	37	37.7	38.5	25.0	25.7
		BC	8	12.5	12.5	0	0
CML	Unrelated	CP	24	39.7	52.6	39.7	52.6
		AP	17	47.1	50.0	47.1	50.0
		BC	6	33.3	47.1	0	0
NHL	Autologous	CR1	24	-	82.1	-	82.1
		PR	65	-	63.6	-	60.4
		CR2	39	-	57.0	-	53.4
		NR	20	-	-	-	-
NHL	Direct allo		61	50.1	57.5	50.1	57.5
	Prior auto		12	25.0	45.7	-	-
MM	Autologous		88	-	36.0	-	28.8
	Allo MT		14	-	61.4	-	30.7
	Allo NMT		33	-	33.8	-	-

* AML denotes acute myeloid leukaemia, ALL acute lymphoblastic leukaemia, CML chronic myeloid leukaemia, NHL non-Hodgkin's lymphoma, MM multiple myeloma, CR1 first complete remission, CR2 second complete remission, NR not in remission, CP chronic phase, AP accelerated phase, BC blastic crisis, PR partial remission, DFS disease-free survival, and OS overall survival

† Sib: HLA-matched sibling HSCT; Unrelated: HLA-matched unrelated HSCT; Direct alo: directed allogeneic HSCT; Prior auto: prior autologous HSCT; Allo MT: allogeneic myeloablative HSCT; Allo NMT: allogeneic non-myeloablative HSCT

Acute lymphoblastic leukaemia

In 2007, we published our long-term results of allogeneic HSCT for 108 adult ALL patients.[8] Eighty-seven (80.6%) patients had HLA-matched sibling HSCT while the rest (21, 19.4%) had unrelated HSCT. Most of the patients (n=100, 92.6%) had Cy-TBI as conditioning and the remaining had CBV. Not surprisingly, higher incidence of acute graft-versus-host disease (aGVHD) was noted with unrelated HSCT. The incidence of grade 0, 1/2 and 3/4 aGVHD with sibling HSCT were 59.8%, 22.9% and 17.2%, respectively; and with unrelated HSCT were 33.3%, 52.4% and 14.3%, respectively. It is interesting to note that the DFS and OS were higher in patients with grade 1/2 aGVHD compared with grade 0 or 3/4. While the transplant-related mortality was the same between sibling and unrelated HSCT, the unrelated HSCT was associated with lower relapse rate and higher DFS compared with the sibling group. Our data also indicate better DFS and OS rates with earlier stage of disease (CR1>CR2>NR).

Plasma cell myeloma

A total of 135 patients with MM received autologous, myeloablative allogenic and non-myeloablative allogeneic HSCT (88, 14, and 33, respectively) showing no significant difference in OS. Nevertheless, with the small number of myeloablative allogeneic HSCTs, patients younger than 40 years (n=9) has significantly better OS than those over 40 years (n=5) [P<0.015]. This perhaps leaves the controversy of whether allogenic

HSCT is indicated for MM open for discussion.

Recently, we have just completed a study in 24 patients using conventional VAD (vincristine, adriamycin, dexamethasone) thrice as induction treatment. After VAD treatment, patients with paraprotein response over 75% were to receive autologous PBSCT with melphalan 200 mg/m^2 conditioning. Patients with less than 75% response were then salvaged with combination chemotherapy of bortezomib, thalidomide and dexamethasone (VTD) four times before autologous PBSCT. Preliminary results indicate improved response could be achieved with VTD salvage, and autologous PBSCT further enhanced CR rate. Encouraged by such results and those of Oakervee et al,[9] we have started on a new PAD study incorporating bortezomib into first-line therapy followed by autologous HSCT.

Conclusion

Over the years, we have certainly seen a changing trend in HSCT in Hong Kong with increasing use of PBSCT especially in autologous HSCT, increasing use of unrelated donor and cord blood, marked reduction in HSCT for CML but increasing numbers for MM. It is of utmost importance that the role of HSCT should always be considered in the light of other advances in treatment of haematological diseases, so that patients may benefit most from a well-planned treatment strategy and suffer the least of morbidity and mortality.

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