

Adult Allogeneic Bone Marrow Transplantation : Initial Experience in the University Hospital, Kuala Lumpur

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Summary

Prior to 1993, bone marrow transplantation for adult patients was not available in Malaysia. Adult allogeneic bone marrow transplantation commenced in Malaysia when the first transplant was conducted at the University Hospital, Kuala Lumpur on 2 November 1993. Up till July 1995, 10 adult bone marrow transplants had been conducted at the University Hospital. Five patients had acute myeloid leukaemia in first remission, 4 had chronic myeloid leukaemia and 1 had acute lymphoblastic leukaemia in first partial remission. The age range of patients at the time of transplant is 16-40 years (mean 25.5 years). All patients engrafted successfully and the survival for the first 100 days post-transplant is 90%. One patient demonstrated haematological relapse post-transplant but achieved remission with donor buffy-coat infusion. The mean drug cost incurred was RM28,269 for the first 100 days. Locally available adult allogeneic bone marrow transplantation is safe, affordable and has comparable results with reputable overseas transplant centres.

Key Words: Bone marrow transplantation, Adult, Allogeneic, Leukaemia.

Introduction

The first human allogeneic bone marrow transplant was described by Don Thomas in 1957¹. In 1995, bone marrow transplantation is no longer experimental and is firmly entrenched as a potentially curative therapy for leukaemia, aplastic anaemia, malignant lymphomas, other malignant and non-malignant haematological diseases and immunological disorders. Over 15,000 transplants have been recorded in the International Bone Marrow Transplant Registry, and annually, over 5,000 transplants are performed². The first bone marrow transplant in Malaysia was conducted in a paediatric patient at the University Hospital, Kuala Lumpur in 1987³. Prior to 1993 however, bone marrow transplantation was not locally available for adult Malaysian patients, who had to be

referred to overseas centres for transplantation costing approximately RM200,000 per patient, a sum beyond the reach of most individuals. In November 1993, we conducted the first allogeneic bone marrow transplantation in Malaysia on an adult patient. We report the results of the first ten transplants performed in the period November 1993 to July 1995.

Material and Methods

Patients were considered eligible for bone marrow transplantation if they were not older than 40 years and had a fully HLA A, B, DR matched sibling. Disease entities considered suitable include acute myeloid leukaemia in first remission (excluding AML FAB M3) or beyond, acute lymphoblastic leukaemia in first remission with poor prognostic characteristics (e.g.

Philadelphia chromosome positivity) or beyond, chronic myeloid leukaemia preferably in first chronic phase and severe aplastic anaemia.

Informed consent was obtained from both patient and donor prior to the transplant. All patients had a double lumen Hickman catheter inserted either under local or general anaesthesia prior to the transplant.

Oral busulphan 16 mg/kg and IV cyclophosphamide 120 mg/kg was employed as conditioning chemotherapy according to Tutschka *et al*⁴. Low dose standard heparin was used for prophylaxis against hepatic veno-occlusive disease from day -8 to day +21 of transplant. Fluconazole and norfloxacin were administered from day -8 to day +21 for prophylaxis against fungal and gram-negative infections respectively. Acyclovir was given from day 0 to day +21 to prevent Herpes simplex infection. Cotrimoxazole was administered as prophylaxis against pneumocystis carinii pneumonia from day -8 to day -1 and maintained from day +21 as long as the patient was on cyclosporin. Ganciclovir was administered three times a week from day +21 to day +84 as prophylaxis against cytomegalovirus infection.

Patients were nursed in a single room and body substance isolation together with strict hand washing were the main aseptic precautions undertaken. Neither laminar air flow nor HEPA filtration was utilised.

All cellular blood products (excluding marrow) were irradiated and bedside leucocyte filters were used when cellular blood products (excluding marrow) were transfused. Platelet concentrates were electively transfused if the platelet count was less than $20 \times 10^9/l$ or if the patient demonstrated active bleeding e.g. new petechiae or mucosal bleeding. Packed cells were transfused when the haemoglobin concentration was less than 80g/l.

Methotrexate and cyclosporin were used as prophylaxis against graft-versus-host disease. Methotrexate was given at a dose of 7.5 mg/m^2 IV bolus on days +1, +3, +6 and +11 of transplant. Cyclosporin was commenced on day -1 of transplant, and at day +50, the dose was tapered by about 5% per week. The rate of taper was increased starting at day +42 if the patient was considered at high risk of relapse.

All donors underwent bone marrow harvest under general anaesthesia. The marrow was harvested and collected in an aseptic manner using a disposable marrow collection set (Baxter Healthcare). The marrow was transfused via the Hickman catheter soon after on the same day if it was not required to be manipulated. If the marrow required manipulation (in the case of minor or major ABO mismatch), a Baxter CS3000 cell separator was used for red cell depletion or plasma deletion of the donor marrow. Autologous blood transfusion was used for all bone marrow donors in order to maximise safety for the donor.

Nine patients received myeloid growth factors post-transplant. 7 received GM-CSF from day +1 to day +21 (or when the WBC increased to more than $1.0 \times 10^9/l$ on three occasions) as part of an open study. Two patients were enrolled in the ongoing Asia Pacific G-CSF study and one was randomised to G-CSF whereas the other was randomised to control. The patient with acute lymphoblastic leukaemia received G-CSF electively.

Check bone marrow examination to evaluate the status of the graft was performed routinely on day +21 and day +84 post-transplant, and additionally when clinically indicated.

Statistical analysis

Kwikstat 4.1 (Texasoft, USA) was used for all statistical analysis.

Results

Table I summarises the patient and disease characteristics at the time of transplant. The age range of patients is 16 to 40 years with a mean of 25.5 years. 5 patients had acute myeloid leukaemia in first remission, 4 had chronic myeloid leukaemia and 1 had acute lymphoblastic leukaemia in first partial remission. The latter, patient #009, is a 17-year-old girl with bcr-abl positive ALL who only achieved partial remission with mitoxantrone and high dose cytosine arabinoside after intensive chemotherapy with the German BFM protocol failed to achieve response.

Eight patients underwent allogeneic bone marrow transplant from a HLA identical sibling and 2 patients

Table I
Patient and disease characteristics at the time of transplant

Patient No.	001	002	003	004	005	006	007	008	009	010
Age (yrs)	16	19	21	29	27	25	35	26	17	40
Sex	F	M	F	M	M	F	F	M	F	M
Race ¹	C	M	M	M	C	C	M	I	M	I
Diagnosis ²	AML CR1	CML CP1	AML CR1	AML CR1	AML CR1	AML CR1	CML CP1	CML CP1	ALL PR1	CML CP1
CMV ³ status of recipient	positive	positive	positive	positive	positive	positive	positive	positive	positive	negative
ABO donor-recipient match	match	minor ABO mismatch	major ABO mismatch	match	match	match	match	match	ABO match,	match
									minor Rh mismatch	

1. M=Malaya, C=Chinese, I=Indian

2. AML=Acute myeloid leukaemia, CML=Chronic myeloid leukaemia, ALL=Acute lymphoblastic leukaemia, CR1=In first complete remission, CP1=In first chronic phase, PR1=In first partial remission

3. CMV=Cytomegalovirus serology (IgG)

underwent syngeneic transplant using marrow from an identical twin. Table II. summarises the pre- and post-transplant related data.

Engraftment and transfusion requirements

All patients demonstrated stable engraftment. The mean time to stable white cell increment above $1.0 \times 10^9/l$ is 16.7 days (95% C.I. 13.5 to 19.8). The mean time to stable platelet increment above $30 \times 10^9/l$ is 26.4 days (95% C.I. 11.5 to 41.2 days). The mean time to platelet increment was considerably skewed by the delayed platelet engraftment demonstrated by patient #002 who developed immune mediated thrombocytopenia post-transplant which eventually responded to intravenous gammaglobulin. This patient, who had CML pre-transplant, continues to demonstrate stable engraftment with donor karyotype negative for Philadelphia chromosome at day +712 post-transplant.

The mean number of random donor platelet concentrates transfused per patient in the first hundred days is 28.6 (range 2-67). 4 patients received apheresed platelets in addition to random donor platelets. This

was because of insufficient blood bank resources rather than platelet alloimmunization. The mean number of packed cells transfused is 3.4. 5 patients did not require any packed cell transfusions.

Infections

The mean number of septic episodes per patient (defined as microbiologically proven infection or a febrile episode requiring antibiotics) is 2.3 for the first 100 days. The majority of episodes were febrile neutropaenic episodes which occurred during the early transplant period. Blood cultures were positive with mainly gram-negative bacteria during the neutropaenic phase and gram-positive bacteria due to Hickman line related infections. There were no instances of fungal, PCP or CMV infection. One patient, #004, developed Herpes zoster infection (S2 dermatome) on day +412. This patient was still on immunosuppressants for chronic GVHD at that time.

Graft-versus-host disease

Acute GVHD grade 2 or more occurred in 3 out of 10 patients. Patient #005 developed grade 2 cutaneous GVHD on day +14. Patient #008 developed acute

Table II
Transplant related data and outcome

Patient No.	001	002	003	004	005	006	007	008	009	010
Type of transplant	allogeneic	allogeneic	allogeneic	allogeneic	allogeneic	syngeneic	syngeneic	allogeneic	allogeneic	allogeneic
Corrected nucleated cell dose ($\times 10^9/\text{kg}$)	1.6	2.1	1.1	1.2	3.2	0.7	1.6	1.1	3.9	1.0
Days to white cell count $> 1 \times 10^9/\text{l}$	15	28	18	11	16	14	16	18	15	16
Days to self-sustaining platelets $> 30 \times 10^9/\text{l}$	13	82	32	11	26	16	25	27	16	16
No. of platelet con. transfused	10	67	34	11	26	40	30	2	11	55
No. of single donor platelets	0	9	3	0	0	1	0	4	0	0
No. of packed cells	2	12	11	0	6	0	3	0	0	0
Acute GVHD \geq grade 2	nil	nil	nil	nil	yes (skin)	nil	nil	yes (GIT)	nil	yes (skin + GIT)
No. of Infections first 100 days	2	3	3	2	5	2	2	0	1	3
Pneumonitis	nil	nil	nil	nil	nil	nil	nil	nil	nil	yes (non-specific)
CMV Infection	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil
Weeks of follow-up (at 31.12.95)	113	102	86	76	63	52	45	36	29	15
Drug cost (RM)	19,595	44,056	38,979	22,378	48,935	14,300	16,142	28,128	16,010	34,172
Transplant outcome	Alive in CR ¹	Alive in CR	Alive in HR ²	Alive in CR	Alive in 2nd CR ³	Dead				

1. CR=Complete remission

2. HR=Haematological remission, cytogenetic relapse

3. Patient demonstrated haematological relapse but regained continuing remission following donor lymphocyte infusion

GVHD of the gut on day +18 manifesting as severe diarrhoea. Both these episodes responded well to the addition of steroids. Patient #010 developed severe cutaneous and gut GVHD and despite increased immunosuppression, deteriorated and developed fatal pneumonitis. Post-mortem lung biopsy revealed only non-specific pneumonitis.

Only one patient to date (#004), has developed chronic GVHD, manifesting in this case as oral GVHD requiring prolonged immunosuppression.

Hepatic veno-occlusive disease

There was no instance of hepatic veno-occlusive disease.

Transplant outcome

The median follow-up duration is 57.5 weeks (range 15-113 weeks). The actuarial survival, depicted in Figure 1, is 90% at two years. One patient, #007, developed cytogenetic relapse at day +100 when cytogenetic analysis of the marrow revealed that 2/4 metaphases were Philadelphia positive. This patient is currently being treated with s/c α -interferon and is in haematological remission at the time of analysis. Patient #009, developed haematological relapse at day +51 but reattained complete remission following two courses of donor lymphocyte infusion. The remaining surviving 7 patients are free of disease.

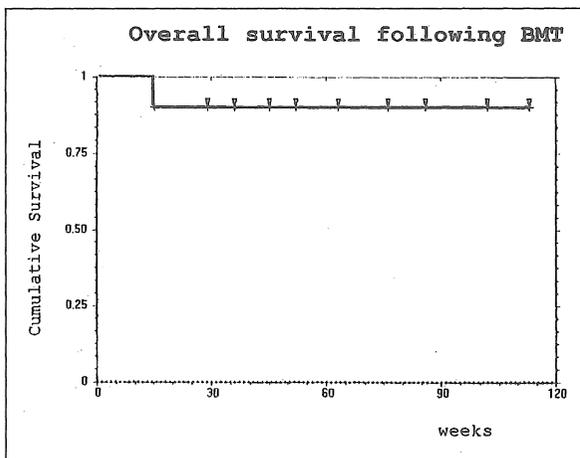


Fig. 1: Tick marks represent time-censored patients

Cost of BMT

The mean drug cost incurred for the first 100 days is RM 28,269 (range RM 14,300 - 48,935). It is estimated that the total cost of BMT per patient is between RM 30,000-60,000 if drug costs, consumables, ward and other hospital costs are taken into account.

Discussion

The outcome of transplantation in this group of patients compares very favourably with those of reputable overseas centres, although longer follow-up and a larger number of patients are required for a more meaningful comparison. In good risk patients (AML in first CR and CML in first chronic phase), one now expects 5 year disease free survival of up to 70%⁵.

A 10% transplant related mortality falls within accepted limits as does a 30% incidence of acute graft versus-host-disease. There appears to be a low incidence of chronic GVHD (10%) and on the whole morbidity from GVHD is low but again, larger numbers of patients and longer follow-up are required in order to determine a more accurate incidence.

One may argue that the favourable outcome reflects a selected group of patients. For instance, increasing age is associated with increased transplant morbidity and mortality, largely from graft-versus-host-disease. The upper age limit in this initial cohort of local patients is 40 years, whereas it is now 55 years in many overseas centres. This group of patients also had relatively good risk disease and only one patient had poor prognostic features. While local transplant resources remain limited, it may not be unreasonable to pursue such a selective policy as it would limit transplant to patients who would benefit the most in terms of having the highest chance of disease free survival.

Amongst clinicians, there still remains some controversy as to whether patients with AML should be transplanted in first remission. While some may pursue a line of intensive consolidation chemotherapy and reserve transplantation for those patients who relapse, one must

bear in mind that it remains an optimistic assumption that 30-40% of patients with AML may be cured with intensive chemotherapy and an additional 20-30% cured by BMT as a salvage procedure giving a total of about 60% cured by this approach⁶. In the local context, some other factors should be considered in deciding who should be transplanted. Early detection of relapse for instance may not be easy for many reasons. Identification of good risk patients with AML who might benefit from intensive chemotherapy alone requires cytogenetic analysis (e.g. identification of inv(16) or t(8;21)) which unfortunately is not readily available in most parts of Malaysia. Acute promyelocytic leukaemia (AML FAB M3) which is usually readily identified by morphology does not require demonstration of t(15;17) for diagnosis except in difficult cases. We did not include patients with acute promyelocytic leukaemia in first remission because of the good results obtained with tretinoin as induction therapy followed by consolidation chemotherapy giving a five year survival of more than 70% as experienced by this centre⁷. We chose to transplant these patients only in relapse.

Many patients with acute lymphoblastic leukaemia are cured by chemotherapy alone, an experience also supported by local data⁸. We therefore restricted transplantation in patients with ALL for those who demonstrated poor prognostic features (e.g. t(9;22) or bcr-abl positive, t(4; 11)), or who relapsed post-chemotherapy.

Bone marrow transplantation continues to evolve and is achieving better results over the years⁵. For instance, prophylactic use of ganciclovir, as in our group of patients, has virtually eradicated CMV infection and CMV pneumonitis which used to be a major source

of morbidity and mortality⁹. It represents a major advance particularly for the population in Malaysia with a high seropositive rate for CMV, a situation in which one might expect a relatively high incidence of CMV post-transplantation as a result of viral reactivation. Refinements to this in the future may be close surveillance for CMV excretion and the use of ganciclovir as pre-emptive treatment rather than as prophylaxis.

The problem of relapse following transplant is being addressed to some extent with the understanding of the graft-versus-leukaemia (GVL) effect. This very lack of GVL in our patient who underwent a syngeneic transplant for CML was probably the reason for the cytogenetic relapse post-transplant. The use of donor lymphocytes to induce GVL and indeed overcome haematological relapse following transplant is well illustrated in our patient who was transplanted for ALL in partial remission. Such an approach may be further refined with the clarification of cell dose required and the clinical separation of GVL from GVHD¹⁰. The use of peripheral stem cells in the allogeneic setting is another approach which promises to further enhance the outcome of transplantation in the future¹¹.

In conclusion, we have shown that adult allogeneic bone marrow transplantation is perfectly feasible in the local setting. While it remains an expensive form of therapy, it represents an important advance in locally available curative treatment for leukaemia. In terms of cost effectiveness, it also means considerable savings in view of the higher cost of bone marrow transplantation performed at reputable overseas centres.

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