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Bone marrow transplantation for children with acute myelogenous leukaemia in the first complete remission

T. Matsuyama [a,*], K. Horibe [a,b], K. Kato [a], S Kojima [a,b]

[a] *Division of Haematology/Oncology, Children's Medical Center, Japanese Red Cross, Nagoya First Hospital, 3–35 Michishita-cho, Nakamura-ku, Nagoya City, 453 Japan*

[b] *Department of Paediatrics, Nagoya University School of Medicine, Nagoya, Japan*

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Abstract

Of 52 children aged 9 months to 16 years old with acute myelogenous leukaemia (AML) in first complete remission undergoing bone marrow transplantation at our institution, 31 received allogeneic transplants (allo-BMT) and 21 received autologous transplants (ABMT). Initial induction and consolidation chemotherapy were not uniform. BMT was performed at a median of 7 months (range: 2.5 to 22.5 months) from the diagnosis. Conditioning included chemotherapy ($n=43$: 4×4 mg/kg of busulfan and 3×60 to 70 mg/m^2 of melphalan) or total body irradiation (12 Gy) plus chemotherapy ($n=9$). Graft-versus-host disease (GVHD) prophylaxis in allo-BMT cases consisted of methotrexate ± cyclosporin A. Unpurged marrow was used in ABMT cases. All patients showed sustained engraftment. Amongst allograft cases, acute or chronic GVHD developed in 7 patients each (23%). 8 patients (15%) died (5 with allo-BMT, 3 with ABMT), including transplant-related mortality in 3 of the allo-BMT patients. 7 patients had relapses (3 with allo-BMT, 4 with ABMT). As of June 1999, 43 patients are alive and well 13 to 160 months after BMT (median, 71), with 5-year disease-free survival rates after BMT of 84% for allo-BMT, 81% for ABMT and 83% altogether. Although the presented data are based on a retrospective evaluation, we consider BMT for childhood AML during first complete remission an effective treatment for eradicating leukaemia.

Keywords: Childhood; Bone marrow transplantation; Acute myelogenous leukaemia; Melphalan; First complete remission

1. Introduction

Current conventional chemotherapy has improved the survival of children with newly diagnosed acute myelogenous leukaemia (AML), but difficulties persist in maintaining long-term disease-free survival. The best treatment for AML patients upon achievement of an initial complete remission (CR) is uncertain. Whilst bone marrow transplantation (BMT) is an important option at this point, controversy has arisen regarding BMT for children in their first CR. Associated with a low relapse rate [1,2], allogeneic-BMT (allo-BMT) has proven superior to autologous BMT (ABMT) in some trials [1–3]. However other studies [4,5] have failed to demonstrate a difference between allo-BMT and ABMT. We present the experience based on a retrospective evaluation at our own institution of treating children with AML in their first CR with allo-BMT and ABMT.

2. Patients and methods

52 children received either an allogeneic or an autologous BMT whilst experiencing their first CR between February 1986 and May 1998 (Table 1). The median age was 7 years (range: 9 months to 16 years). Half of the patients ($n=26$) were referred from other hospitals. The patients had not been treated with a uniform induction/consolidation chemotherapy regimen; 34 (65%) (16 allo-BMT, 18 ABMT) were treated according to the Kousei-Shou ANLL91 protocol [6]. These patients were incorporated into our allo-BMT and ABMT programme during their consolidation phase. Other patients were treated according to local protocols consisting mainly of combinations of VP-16, AraC and anthracycline.

* Corresponding author. Tel.: +81-52-481-5111; fax: +81-52-482-7733.

E-mail address: matsujii@nagoya-1st.jrc.or.jp (T. Matsuyama).

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2.1. Graft-versus-host disease (GVHD) prophylaxis in allo-BMT

23 patients receiving transplants from HLA-matched sibling donors were given methotrexate (MTX) alone (15 mg/m^2 on day 1, and 10 mg/m^2 on days 3, 6, 11, and subsequently once weekly until day 60). Patients receiving transplants from a phenotypically HLA-identical related or unrelated donor, 1 patient receiving a transplant from an HLA-matched sibling donor, and 1 patient receiving a transplant with an HLA 1-locus mismatch from his father received cyclosporin A (CsA) combined with a short course of MTX. CsA was administered intravenously (i.v.) 3 mg/kg on day 3 or 5. After 1 or 2 months, oral CsA at a dose of 5 or 6 mg/kg was substituted for the i.v. CsA for 6 months and thereafter the dose was reduced until discontinuation approximately 1 year after BMT. The short course of MTX consisted of an initial four infusions if the graft was from a related donor or five infusions if the graft was from an unrelated donor. For prevention of mucositis, folinic acid (3 mg) was given in divided oral doses and also intravenously (3 mg) on the day following MTX administration (Table 2).

2.2. Bone marrow procedures in ABMT

Marrow was harvested after the last course of consolidation chemotherapy just before the beginning of the conditioning regimen. Marrow cells were untreated and cryopreserved with 10% dimethyl sulphoxide (DMSO) using a programmed rate freezer and stored in liquid nitrogen. After thawing the cells were infused rapidly without removal of DMSO.

Table 1
Patient characteristics

			n (%)
Allogeneic transplant			31 (60)
HLA-matched			
Sibling			24 (46)
Family			4 (8)
Unrelated volunteer			2 (4)
HLA 1 locus mismatched family			1 (2)
Autologous transplant			21 (40)
FAB subtype	Allogeneic	Autologous	Total
	n (%)	*n* (%)	*n* (%)
	31, 7[a] (60)	21 (40)	52 (100)
M0	1 (3)	0	1 (2)
M1	8, 3[a] (26)	2 (10)	10 (19)
M2	11, 3[a] (35)	9 (43)	20 (38)
M3	2 (6)	0	2 (4)
M4	4, 1[a] (13)	1 (5)	5 (10)
M5	3 (10)	2 (10)	5 (10)
M7	2 (6)	7 (33)	9 (17)
Interval (months) from diagnosis to transplant			
<6	8, 2[a] (26)	0 (0)	8 (15)
6 to <9	16, 2[a] (52)	18 (86)	34 (65)
$\geqslant 9$	7, 3[a] (23)	3 (14)	10 (19)
Median (range)	6	7	7 (2.5–22.5)
Gender			
Male	12, 3[a] (39)	4 (19)	16
Female	19, 4[a] (61)	17 (81)	36
Age (years)			
<2	4, 1[a] (13)	5 (24)	9 (17)
2 to <10	17, 4[a] (55)	6 (29)	23 (44)
$\geqslant 10$	10, 2[a] (32)	10 (48)	20 (38)
Median (range)	6.9	7.1	7.0 (9 months–16 years)
Conditioning regimens			
L-PAM + Bu	22, 3[a] (71)	21 (100)	43, 3[a] (83)
L-PAM + Bu + TBI	3, 1[a] (10)		3, 1[a] (6)
L-PAM + TBI	3, 2[a] (10)		3, 2[a] (6)
CY + TBI	1 (3)		1 (2)
CY + AraC + TBI	2, 1[a] (6)		2, 1[a] (4)

[a] Indicate the number of HLA-matched transplants from donors other than a sibling. Bu was administered at 1 mg/kg or 35 mg/m^2×4×4 or 2 days for cases with TBI.

L-PAM, melphalan; Bu, busulfan; CY, cyclophosphamide; AraC, cytosine arabinoside; TBI, total body irradiation.

2.3. Transplantation procedure

Conditioning regimens consisted of either busulfan/melphalan ($n=43$, 83%) or total body irradiation (TBI) with high-dose chemotherapy ($n=9$, 17%; Table 1). Busulfan (Bu) was administered orally 4 times a day for 4 days in cases without TBI and for 2 days in cases with TBI. Bu usually was given at a dose of 1 mg/kg, but for patients younger than 5 years or with less than 1 m^2 of body surface, Bu was given at a dosage of 35 mg/m^2. Phenobarbital or sodium valproate was given for 5 or 7 days beginning the day before Bu initiation. The day following the last dose of Bu, melphalan (L-PAM) was given at a dose of 60 to 70 mg/m^2 (maximal dose, 100 mg) i.v. for 3 days. TBI was delivered at a dose of 12 Gy (3 Gy/fraction, twice a day for 2 days). Cyclophosphamide (CY) was given at 60 mg/kg/day for 2 days. Cytosine arabinoside (AraC) was given as a total dose of 8 g/m^2 over 3 days. The median number of nucleated marrow cells infused was 4.2×10^8/kg (range: 3.3 to 7.5×10^8) for allo-BMT and 0.6×10^8/kg (range: 0.08 to 4.2×10^8) for ABMT (Table 3). Marrow infusions were performed at a median of 7 months (range: 2.5 to 22.5) following diagnosis (Table 1).

The benefits and risks of the transplantation procedure were explained to parents in advance, and informed consent was obtained before BMT.

2.4. Supportive care

Transplantation was performed in a laminar airflow room, and fosfomycin was given from 7 days before transplant until granulocyte recovery was demonstrated. G-CSF was used in 2 patients undergoing allo-BMT and 6 patients undergoing ABMT who developed serious infections, beginning no sooner than day 9 after BMT. All patients received oral sulphamethoxazole, trimethoprim and amphotericin B beginning at least 3 days before BMT and continuing until 1 year after transplantation. Oral acyclovir at a dose of 300 to 1000 mg was given daily, and anti-cytomegalovirus immunoglobulin was given at a dose of 2.5 to 5 g weekly until 90 days after transplantation, except in 2 patients who were treated early in the study period.

2.5. Statistical methods

All results were analysed as of 30 June 1999. Disease-free survival (DFS) was defined as the time from BMT to relapse or death, and was estimated using the Kaplan–Meier product-limit technique. Haematological reconstitution between allo-BMT group and ABMT group was compared using the Wilcoxon test and complications were compared

3. Results

3.1. Engraftment

Engraftment was achieved in all patients. The median time to engraftment was significantly longer in the ABMT group than in the allo-BMT group ($P<0.001$; Table 3). Three patients who underwent ABMT

Table 2
Graft-versus-host disease (GVHD)

Prophylaxis	MTX[a] (%)	MTX[b] + CsA (%)	Total				
n of patients	23 (74)	8 (26)	31				
L-PAM + Bu	19 (86)	2 (14)	22				
L-PAM + Bu + TBI	2 (67)	1 (33)	3				
L-PAM + TBI	1 (33)	2 (67)	3				
CY + TBI	1 (100)	0	1				
CY + AraC + TBI	0	2 (100)	2				
Incidence							
	Acute GVHD					HLA	
	L-PAM + Bu $n=22$	TBI group $n=9$	Total $n=31$ (%)	MTX $n=23$	MTX + CsA $n=8$	Matched sibling $n=24$	Other than matched sibling $n=7$
Grade							
I	1	2	3 (10)	2	1	2	1
II + III	2	2	4 (13)	2	2	2	2
Total	3	4	7 (23)	4	3	4	3
	Chronic GVHD[c]						
	5	2	7 (23)	6	1	6	1

Bu, busulfan; L-PMA, melphalan; TBI, total body irradiation; CY, cyclophosphamide; AraC, cytosine arabinoside; MTX, methotrexate; CsA, cyclosporin A.

[a] MTX alone was given until day 60.

[b] Short-course MTX consisted of an initial four infusions (related donor) or five infusions (unrelated donor).

[c] Based on patients surviving more than 3 months.

required more than 2 months for haematological recovery (granulocytes $\geqslant 500$ and no need of platelet transfusion). Little difference between patients receiving and not receiving G-CSF was seen with respect to haematological recovery.

3.2. GVHD

Acute GVHD developed in 7 of 31 (23%) allogeneic transplant recipients (Table 2). Acute GVHD of grades II and III was documented in 3 patients and 1 patient, respectively. Chronic GVHD occurred in 7 of 30 subjects (23%). 3 patients developed both acute and chronic GVHD. Signs of GVHD resolved or improved with administration of steroids, CsA, or tacrolimus in all patients.

3.3. Complications

Fever and liver dysfunction were the most common complications of both allo-BMT and ABMT (Table 4). Fever usually was related to granulocytopenia attributable to the conditioning regimen. Transient liver dysfunction developed almost always within 1 month of BMT, and both peak aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were below 400 IU/L except in 2 patients. No patients demonstrated veno-occlusive disease or cardiac failure. *Herpes zoster* virus infection was noted to occur after cessation of oral acyclovir. One of 2 patients who did not receive acyclovir developed *H. zoster* infection 88 days after BMT. Interstitial pneumonitis (IP) occurred in 7 patients, 6 of whom developed it between 1.5 and 3 months after their BMT. Haemorrhagic cystitis appeared 50 days after BMT in 2 of 3 patients. Except for some pulmonary complications, these disorders responded to appropriate therapy or subsided spontaneously. No significant differences in the incidence of complications were noted between allogeneic and autologous BMT groups except for liver dysfunction ($P < 0.05$) and IP ($P < 0.05$).

3.4. Relapse and causes of death (Table 4)

Seven patients (3 with allo-BMT, 4 with ABMT) had relapses between 2 and 15 months alter BMT (median: 8 months). Relapse could not be predicted from FAB subtype and white blood cell count at diagnosis. Transplant-related mortality (TRM) occurred in 3 patients, 1 of whom received a second BMT after relapse and died from obstructive bronchiolitis whilst experiencing a CR. Amongst 7 patients whose donor was other than an HLA-identical sibling, 1 died of IP. Allo-BMT was associated with a somewhat lower relapse rate (10 versus 19%, not significant) and a somewhat higher TRM than ABMT (10% versus 0, not significant).

3.5. Survival

43 patients remained disease-free at a median of 70 months from BMT (range: 13 to 160). No relapse occurred beyond 2 years after BMT. Overall survival and DFS rates (Fig. 1) at 5 years for all patients were 84 and 83%, respectively. DFS rates for allogeneic and autologous BMT were 84 and 81%, respectively, which were not significant (Fig. 2). DFS rates for TBI ($n=9$) and non-TBI ($n=22$) groups amongst allo-BMT patients were 78 and 86%, respectively (not significant). Of 2 patients undergone transplants from unrelated donors, 1 is alive and well, but the other developed grade II acute GVHD and died of IP.

Table 3
Haematological reconstitution

		Days to haemopoietic recovery			
	Infused cells $\times 10^8$/kg	WBC $>1000/\mu l$	Granulocyte $>500/\mu l$	Platelet last transfusion	Reticulocyte $>1\%$
All cases ($n=52$)		10–35	12–78	8–125	13–63
Median ($n=52$)		18	26	35	21.5
Allogeneic ($n=31$)	3.3–7.5	12–35	12–36	8–120	13–39
Median	4.2	18	22*	21*	17*
G-CSF[a] $n=2$	4.3, 4.6	14, 17	14, 17	49, 62	14, 26
TBI ($n=9$)	3.3–7.5	12–23	12–36	8–120	13–39
Median	3.9	17	18	26	22
Non-TBI ($n=22$)	3.3–5.9	13–35	14–35	11–49	13–25
Median	4.3	18	22	19	17
Autologous ($n=21$)	0.08–4.2	10–29	12–78	35–125	16–63
Median	0.6	19	34*	56.5*	34*
G-CSF $n=6$	0.15–1.6	12–29	12–78	48–112	24–49
Median	0.4	20.5	31.5	54	33.5

*$P < 0.001$.

[a] G-CSF was initiated no sooner than day 9 after bone marrow transplant, only in patients with a severe infection.

WBC, white blood cell; TBI, total body irradiation; G-CSF, granulocyte-colony stimulating factor.

Table 4
Complications and causes of death

	Allogeneic ($n=31$)		Autologous ($n=21$)	Total
	L-PAM + Bu $n=22$	TBI group $n=9$	L-PAM + Bu	$n=52$ (%)
Complications				
Fever	12	7	17	36 (69)
Herpes zoster infection	2	2	4	8 (15)
CMV infection (except IP)	1	1		2 (4)
Stomatitis (≥WHO grade III)	2	2	3	7 (13)
Vomiting (≥WHO grade III)	4			4 (8)
Severe diarrhoea	1	1		2 (4)
Liver dysfunction*,[b]	15	6	6	27 (52)
Haemorrhagic cystitis	3			3 (6)
Renal dysfunction		2		2 (4)
TMA	1	1		2 (4)
IP*	3	4		7 (13)
Pneumonia	3			3 (6)
Transient thrombocytopenia[a]	3		3	6 (12)
Causes of death				
Relapse	1	1	3	5 (10)
IP		1		1 (2)
Obstructive bronchiolitis	2			2 (4)
Total	3	2	3	8 (15)

*Allogeneic versus Autologous $P<0.05$.
[a] After haematological recovery.
[b] Both AST and ALT level ≥100 IU/L.
L-PAM, melphalan; Bu, busulfan; TBI, total body irradiation; CMV, cytomegalovirus; IP, intersitial pneumonitis; TMA, thrombotic microangiopathy.

4. Discussion

Recent developments in intensive treatment for AML have represented considerable advances. The survival rates for AML patients in low risk groups such as FAB M2 with a white blood cell count $<20\,000/\mu L$, FAB M3 and FAB M4 with eosinophilia [7] now range from 78 [8] to 91% [7]. However, chemotherapy alone is not adequate in higher risk groups, and BMT during the first CR is still regarded as the treatment of choice for childhood AML. In the report of the EBMT Pediatric-Diseases Working Party [9], patients with AML

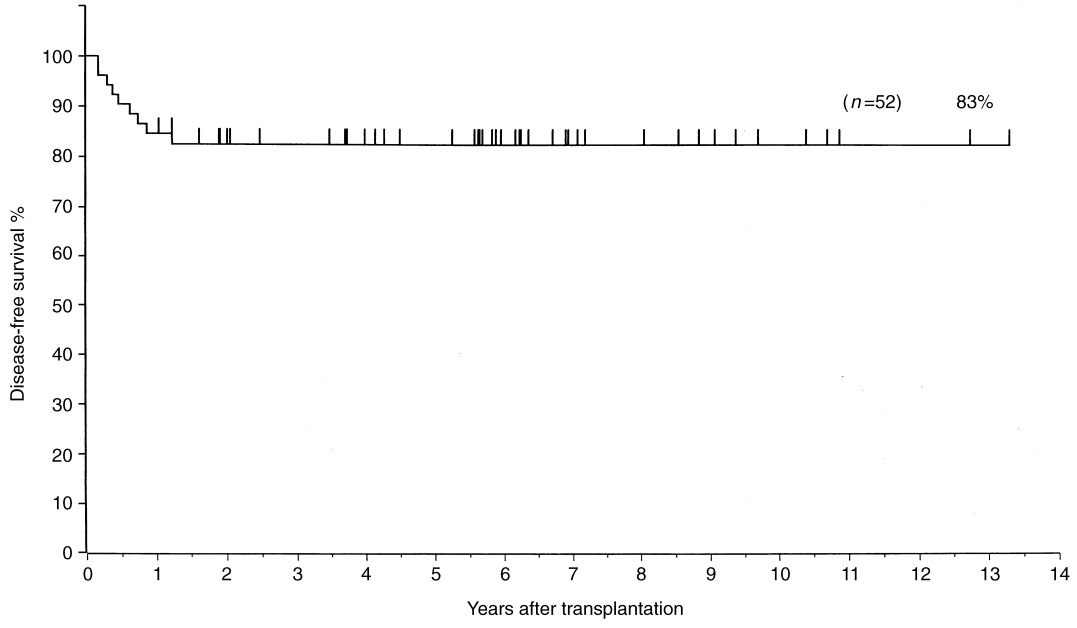

Fig. 1. Disease-free survival for all 52 patients.

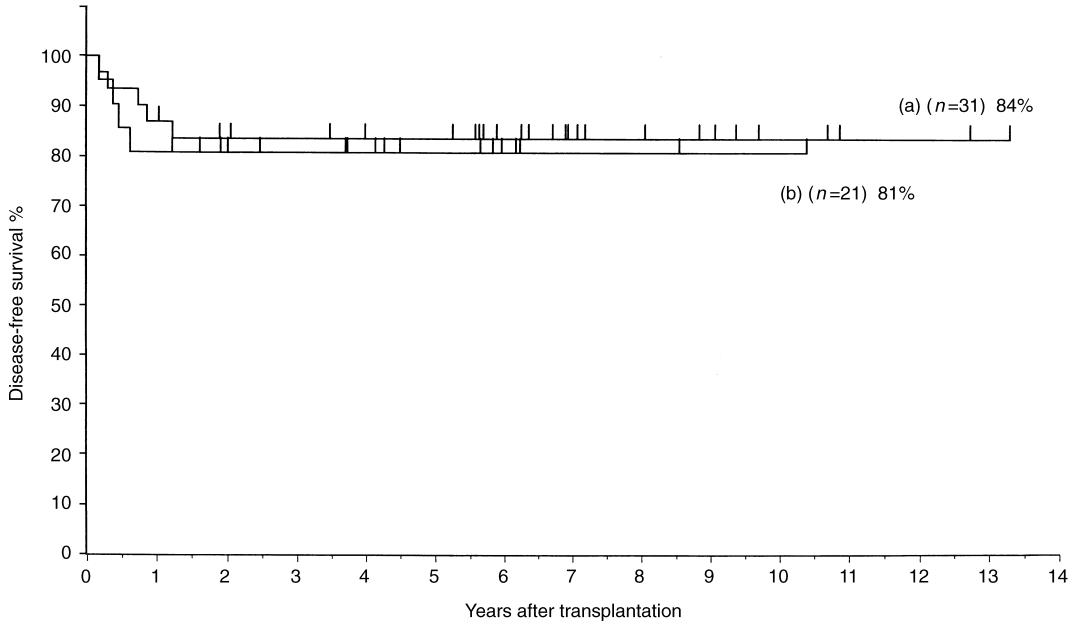

Fig. 2. Disease-free survival from the day of transplant for 3l patients undergoing allogeneic (a) and 21 patients undergoing autologous bone marrow transplantation (b).

experiencing their first CR were considered candidates for BMT, even though the procedure was not considered mandatory. Children with acute lymphoblastic leukaemia who relapse after modern intensive treatment may be inclined to relapse and show limited leukaemia-free survival even after BMT from HLA-matched siblings [10]. Stahnke and colleagues [11] reported that only 26% of patients with AML were alive out of 102 patients who underwent either chemotherapy or BMT after their first relapse. Because of the poor prognosis of BMT after relapse, BMT for AML during the first CR may be acceptable. However, the British Medical Research Council [8] has recently expressed doubt that ABMT should have a major role in treatment during the first CR. Moreover, intensive chemotherapy used in AML 10 was highly effective, possibly reducing the need for allo-BMT. Additional studies will be necessary to resolve the issue of indications for BMT in paediatric patients with AML experiencing their first CR.

Although BMT for children using TBI has resulted in improved survival [12], late sequelae of TBI such as growth impairment have been documented [13]. High-dose L-PAM has been shown to have a potent anti-leukaemic effect against AML [14]. Whilst in general cyclophosphamide (CY) has not been considered as a useful agent in conventional chemotherapy for AML, Tutschka and colleagues [15] have reported encouraging results in adult AML following a regimen of Bu and CY. Since May 1988 Bu with L-PAM has been preferred at our institution. Graft marrow purging in ABMT has been associated with a decreased incidence of relapse [16], especially in patients receiving transplants within 6 months of achieving a CR [17]. TRM in ABMT patients have been linked to slow engraftment attributable to a purged marrow graft [3]. Haematological recovery after ABMT following purging has been found to occur more slowly than after allo-BMT [4,5]. We, therefore, did not purge the marrow for fear of delayed engraftment and rejection. However, marrow engraftment was significantly delayed in our ABMT cases compared with our allo-BMT cases.

Administration of GM-CSF after ABMT for AML has been associated with a high risk of relapse [18]. Whilst G-CSF was not used in most of our patients, no increased tendency toward relapse was demonstrated in our patients who received G-CSF, although G-CSF was given relatively late in the procedure.

Particularly in ABMT, the Italian Association of Pediatric Hematology Oncology [19] has recommended use of TBI, and excellent results have been presented in patients receiving purged marrow combined with TBI and L-PAM [20]. Longer pretransplant intervals and use of L-PAM may account for the good results in our ABMT patients, for whom unpurged marrow was used. Since all of our treatment failures after ABMT were relapses, development of a sensitive method of detecting minimal residual disease at the time of harvest may improve the results of ABMT. The relapse risk observed in allo-BMT was lower than in ABMT, and the survival rate was accordingly better after allo-BMT than ABMT [1,2], but this advantage of allo-BMT was offset by an increased rate of TRM in this group compared with ABMT patients. Our patients undergoing ABMT showed a higher relapse rate than that associated with allo-BMT, but no life-threatening complications occurred. Therefore, as in some other series [4,5], our overall

results showed no differences in DFS between allo-BMT and ABMT. More complications developed in our allo-BMT group than in the ABMT group, although the three instances of TRM documented amongst our allo-BMT patients represent a relatively lower incidence compared with other reports. In larger series [21–23] the incidence of acute GVHD of grade $\geqslant$II was 15 to 38%, representing one of the reasons for treatment failure. Acute GVHD of grades II and III occurred in only 4 of our patients (13%), and acute GVHD was not related to mortality.

As TRM following both allo-BMT and ABMT is generally lower in children than in adults [1], both allo-BMT and ABMT may improve DFS for paediatric AML patients during their first CR. Treatment failure in allo-BMT and ABMT patients in our series was not influenced by the differences in induction and consolidation chemotherapy protocols used initially after diagnosis. All the patients with AML at our institution who were treated from their initial diagnosis maintained CR for 4 to 9 months until they received BMT, although this is less certain for patients from other institutions. Therefore, patients who achieve initial CR and have an HLA-identical sibling or related donor should be given allo-BMT. The remainder should be eligible for ABMT after approximately 6 months of chemotherapy.

DFS rates over 3 years for allogeneic and autologous BMT in paediatric AML patients during their first CR respectively have ranged from 48 to 78%, and 38 to 63% in larger series reported in the literature [1,3,24,25]. However, studies of small numbers of patients have shown better results, with survival rates ranging from 82 [23] to 100% [26] in allo-BMT and 80 [5] to 87% [27] in ABMT without relapse. Vignetti and colleagues [20] have recommended regimens that include TBI in ABMT, whilst Tiedemann and colleagues [27] have demonstrated good results using L-PAM without TBI. Michel and colleagues [23] have reported no differences in the event-free survival following allo-BMT in patients undergoing TBI and patients receiving 16 mg/kg of Bu and 200 mg/kg of CY. Whilst conditioning with high-dose Bu and L-PAM [28] may be an unconventional choice for BMT in childhood, Bu and L-PAM represented a safe conditioning regimen with acceptable toxicity in our paediatric experience. In the present study, we obtained comparable or superior results to those previous reports.

In conclusion, although the role of BMT for AML during the first CR remains controversial, we consider both allogeneic and autologous BMT to be effective treatments for eradicating leukaemia. In this study, late complications such as endocrinological functions such as pubertal development and thyroid function were not investigated. Although a non-TBI regimen consisting of high-dose Bu/L-PAM appears to be valuable. However, Bu is a major cause of ovarian failure [29]. Thus, additional regimens need to be tried to further reduce sequelae following BMT.

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