

Unrelated donor marrow transplantation: an update of the experience of the Italian Bone Marrow Transplant Group (GITMO)

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This paper has already appeared in a journal supplement [*Haematologica* 2000; 85(Suppl. to n. 11):30-6].

Background and Objectives. Unrelated donor bone marrow transplant (UD-BMT) has become an attractive alternative source of hematopoietic cells for patients lacking a matched sibling. The aim of this paper was to report on results of the 696 UD BMTs performed in 31 Italian institutions during the first 10 years of activity of the Italian Bone Marrow Donor Registry (IBMDR).

Evidence and Information Sources. In 1989 the Italian Bone Marrow Transplant Group (GITMO) established the IBMDR to facilitate donor search and marrow procurement for patients lacking an HLA identical sibling. By end of December 1999, 260,000 HLA-A, B typed volunteer donors had been cumulatively registered and 2,620 searches had been activated for Italian patients. At least one HLA-A, B, DRB1 matched donor was found for 54% of the patients and 696 UD BMTs were performed. In 50% of cases the donor was found in the IBMDR and in 50% in 15 other Registries. The average time from search activation to transplant was 6 months for disease other than CML. For CML it was 14 months. Actuarial 12-month transplant-related mortality (TRM) was 68% in patients grafted between 1979 and 1992 and 44% for patients grafted after 1993. Twenty-eight per cent of patients developed grade III or IV acute GvHD and 24% developed extensive chronic GvHD. The rate of disease free survival at three years was 57% for patients with 1st chronic phase CML, 37% for patients with 1st or 2nd CR

decision making and problem solving

haematologica 2001; 86:451-456

http://www.haematologica.it/2001_05/0451.htm

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ALL, 31% for AML or MDS patients \leq 18 years of age and 54% for patients with inborn errors.

Perspectives. We conclude that the IBMDR has benefited a substantial number of patients lacking a matched sibling and has facilitated the recruitment of UDs into the international donor pool. The long time required for the search is the major obstacle to the success of this programme. This suggests that early transplant and a decrease in TRM could further improve these encouraging results.

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Key words: bone marrow transplant from unrelated donor (UD BMT), Italian Bone Marrow Transplant Group (GITMO), Italian Bone Marrow Donor Registry (IBMDR)

Allogeneic bone marrow transplantation from HLA-identical siblings has become an effective treatment for patients with haematological malignancies, syndromes of marrow failure, and various inborn errors.¹⁻³ Since only one out of three patients has a suitable, matched sibling, several investigators have explored the use of alternative sources of haematopoietic stem cells, including HLA-mismatched family members,⁴ unrelated donors

(MUD),⁵ or cord blood (UCBs) units.⁶

The *Italian Bone Marrow Transplant Group* (GITMO) established the *Italian Bone Marrow Donor Registry* (IBMDR) in 1989 to facilitate donor search and marrow procurement for patients lacking an HLA identical sibling. In 1996 we reported on the initial experience concerning 633 searches activated for Italian patients and 75 BMTs from UDs performed in GITMO institutions.⁵ In this report, we present the results of the initial 696 UD BMTs performed in Italy between September 1989 and December 1999.

Design and Methods

IBMDR

The IBMDR was established as a collaborative effort among the Regional Tissue Typing Laboratories. Its principles and policies are similar to those of other international Registries.⁷⁻¹¹ IBMDR includes 17 local Registries and 100 donor centres for the HLA class I and II serological typing of volunteer donors.

Donor recruitment

In December 1992 the number of donors was 25,000. Over the following years more than 20,000 new donors per year have been added to the registry. Currently, the IBMDR file contains data concerning approximately 260,000 volunteers. All of them are HLA-A,B serologically typed, while HLA-DR serological typing has also been performed on 86,000 (33%) of these registered donors. The DRB1 typing by PCR technique of 11,000 donors is also available. Once a month the IBMDR electronically sends its donor HLA phenotype file to the *Bone Marrow Donors World Wide* (BMDWW) directory, which includes more than 6,000,000 donors in its May 2000 edition.¹²

All the Italian transplant centers (TC) involved in this programme are accredited through the GITMO to the IBMDR, to European Registries and to the *National Marrow Program of the United States of America* (NMDP), according to the *World Marrow Donors Association* standards.

Matching criteria

Before December 1991 most TC based their matching criteria on HLA-A, B, DR identity using serologic testing. After January 1992 class II antigens matching was confirmed by DNA techniques as previously described.⁵

Engraftment

Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) $>0.5 \times 10^9/L$, whereas platelet engraftment was defined as the first of 3 consecutive days with an untransfused platelet count $>50 \times 10^9/L$.

Data collection and statistical analysis

Essential data regarding all donor-recipient pairs, and information concerning the harvesting procedure were obtained by the IBMDR data centre. Information on the BMT procedure and on the recipients follow-up were collected every year by the GITMO Registry. Univariate analysis was performed for relapse, for disease-free survival (DFS), and for transplant-related mortality (TRM). TRM was defined as mortality due to any cause other than disease progression in patients with haematological malignancies. Life tables (Kaplan-Meier estimates) were calculated at 3 years to measure the proportion of patients alive or, for malignancies, alive and disease-free. Data were updated as of December 31st, 1999.

Results

The search

Between September 1st 1988 and December 31st 1999 the search for an UD was started for 2,620 patients. Half of them were activated during the last three years. During the last 12 months, a formal search was started each month for approximately 40 new Italian patients.

Probability of finding a matched donor

At least one HLA-A,B,DRB1 matched donor was found for 54% of the patients. At least one 1 antigen mismatched donor was found for 66% of the patients. At least one HLA-A, B, CW, DRB, DQA, DQB matched donor was found for 28% of the patients.

As of December 1999, 696 Italian patients had undergone UD BMT in one of the 31 TC participating in this program. Three hundred sixty-seven of them were over 18 years of age, while, 329 were 18 years old or less. Half of them were transplanted during the last 25 months. In 1999 each month approximately 15 new Italian patients underwent UD BMT. Details on the activity of the 31 TC are reported in the Appendix. The characteristics of donors and recipients listed according to the type of disease that led to transplant are reported in Table 1.

Donor registries

The first UD BMT performed in Italy was made possible in March 1989 by a donor listed with the Anthony Nolan Research Foundation. The first UD marrow provided by the IBMDR was grafted in March 1991. By December 1999, 347 donors had been provided by the IBMDR and 349 by other Registries, as shown in Table 2. As of 1997 the IBMDR has become the main source of donors for Italian patients.

Donor recipient matching

Six hundred out of 696 pairs were HLA-A,B,DRB1

Table 1. Characteristics of donors and recipients according to the type of disease that led to transplant.

Disease	No. pts.	Age (years)				Gender			
		donor		recipient		donor		recipient	
		md.	r.	md.	r.	M	F	M	F
Neoplastic	601								
CML	251	36	20-58	32	6-52	130	121	169	82
1 st chronic phase	145								
2 nd chronic phase	74								
Accelerated phase	26								
Blast crisis	6								
ALL	192	35	20-57	14	2-49	100	92	127	65
1 st remission	54								
2 nd remission	94								
≥3 rd remission	44								
AML	80	33	21-55	24	2-51	47	33	48	32
1 st remission	30								
2 nd remission	34								
≥3 rd remission	16								
Myelodysplasia	68	39	22-55	17	1-53	36	31	35	33
Other	10	35	28-45	36	9-49	7	3	4	6
NHL	3								
MM	2								
Non neoplastic	95								
Severe aplasia	12	39	24-51	23	4-43	6	6	4	8
Inborn errors	83	35	20-52	4	2-25	45	38	58	25
Severe combined immunodeficient	17								
Non-immunodeficient disorders	66								
TOTAL	696								

CML: Chronic myeloid leukemia; ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; NHL: Non-Hodgkin's lymphoma; MM: Multiple myeloma. md.: median; r.: range; M: male; F: female.

Table 3. Matching by recipient age.

Matching	No. of pairs by recipient age	
	≤ 18 yrs	> 18 yrs
A,B,DRB1 =	253	347
1 A locus antigen ≠	23	8
1 B locus antigen ≠	19	4
1 DRB1 antigen ≠	20	1
> 1 antigen ≠	5	-
Unknown	9	7
Total	329	367

Table 4. Conditioning regimens.

	No. of pts
Neoplastic diseases	601
Radiation containing regimens	414
Non-radiation containing regimens	134
Unknown	53
Non neoplastic diseases	95
Radiation containing regimens	21
Non-radiation containing regimens	62
Unknown	12

Table 2. Registries and donors provided to Italian patients.

IBMDR	347
NMDP USA and Canada	102
A. Nolan	87
German	81
French	43
Dutch	10
Swiss	9
Belgian	5
Austrian	2
Spanish	3
Swedish	2
Australian	1
Finnish	1
Norwegian	1
Taiwanese	1

matched, while 80 pairs were mismatched for at least one antigen. Data concerning the remaining 16 pairs are missing. Details on matching by recipient age are reported in Table 3.

Preparative regimen and graft-versus-host disease (GvHD) prophylaxis

The preparative regimen and GvHD prophylaxis varied depending on the underlying disease, on the transplant centre, and over time. Details are reported in Table 4. Briefly, the preparative regimen for 435 out of 631 patients whose data were available included radiation which was either preceded or followed by one or more drugs. One hundred and ninety six patients were treated with a non-radiation containing regimen. Three hundred and five out of 650 patients, whose data were available, received serotherapy (ATG or Campath 1G) containing GvHD prophylaxis; 308 other patients received non-serotherapy containing GvHD prophylaxis, including cyclosporin (CSA) and short methotrexate. The remaining 37 patients received other GvHD prophylaxis.

Engraftment

Among 643 evaluable patients, the 30 who died within 3 weeks of transplantation were not evaluated for engraftment. Sustained neutrophil engraftment was reached at a median of 18 days (range 10-48) after transplant by 621 evaluable patients. Sustained platelet engraftment was reached at a median of 27 days (range 11-273) by 390 out of 540 evaluable patients.

GvHD

Two hundred and sixty four of 367 evaluable patients >18 years of age (77%) developed grade I (77, 22%), grade II (94, 27%), grade III (50, 15%), or grade IV (43, 13%) GvHD.

Table 5. Timing and causes of transplant related mortality before and after 1992.

Year of BMT	No. of patients			
	1989-1992	37	1993-1999	659
Cause of death	First 100 d After BMT	After 100 d From BMT	First 100 d After BMT	After 100 d From BMT
GvHD	5	1	51	34
Interstitial pneumonia	2	2	31	13
Infections	4	2	24	15
Unknown			23	10
Graft failure	3	1	6	10
Organ Failure			10	6
Haemorrhage	1		8	3
VOD			10	1
Cardiac Failure	1		5	1
2nd tumour	1	1	2	1
Encephalopathy	1	1	1	2
Other			1	1
Total	18	8	172	97

Two hundred and forty four of 329 evaluable patients ≤ 18 years of age (82%) developed grade I (82, 28%), grade II (76, 26%), grade III (51, 17%), or grade IV (35, 11%) GvHD.

Chronic GvHD developed in 148/230 (64%) evaluable patients >18 years of age, and 37 of them (16%) had extensive disease. In patients ≤ 18 years of age it developed in 75/191 (39%) evaluable patients, and 40 of them (21%) had extensive disease.

Transplant-related mortality (TRM)

Altogether 295 out of 696 patients died of TRM. Between 1989 and 1992 18/37 patients died within the first 100 days after BMT and 8 died after 100 days from BMT. Actuarial 12-month TRM was 68% (C.I. 53-82). Between January 1993 and December 1999, 172/659 patients died within the first 100 days after BMT and 97 patients died after 100 days from BMT. Actuarial 12-month TRM was 44% (C.I. 53-82) ($p=0.01$). Timing and causes of TRM are reported in Table 5.

Chronic myeloid leukemia (CML)

Two hundred and fifty one patients with CML underwent UD BMT. The median interval from diagnosis to transplant was 27 months (range 4-119) for 145 patients undergoing BMT in first chronic phase, and 33 months (range 5-130) for 106 patients undergoing BMT in a more advanced phase. The median interval between search activation and transplant was 14 months (range 2-90). Altogether 101 of 251 patients died of TRM. Actuarial 12-month TRM was 38% (CI 33-46).

CML recurrence occurred in 29 patients at a median of 5 months (range 1-59) after BMT. The 3 year

Table 6. DFS of CML patients.

	No. of pts	DFS %	Univariate analysis
Overall	251		
Disease phase			
total	251	45	
early	145	57	
advanced	106	30	$<.001$
Recipient age at BMT (years)			
≤ 34	141	51	
> 34	110	38	0.01
LLA matching			
A,B,DRB1 =	229	48	
1 Ag mismatched	17	29	0.01
Other	5		
TBI			
Yes	183	48	
No	53	35	0.07
Unknown	15		
CMV status			
Donor/recipient Neg	26	56	
Donor/recipient Pos	189	44	NS
Unknown	36		
Donor age (years)			
≤ 40	178	48	
> 40	73	38	NS
Infused Cells ($\times 10^6$ /kg)			
> 3.5	132	49	
≤ 3.5	106	41	NS
Unknown	13		
Donor gender			
M	130	46	
F	121	44	NS

relapse rate was 20% (CI 15-30). Three year DFS from time of transplant was 45% (CI 37-51).

Univariate proportional hazard regression analysis was performed for DFS after stratification of the following variables: disease phase, recipient age, HLA matching, conditioning regimen, number of infused cells, donor gender and age, CMV status.

Univariate analysis showed that early phase at BMT ($p < 0.001$), recipient age < 34 years ($p = 0.01$), and HLA A,B,DRB1 matching ($p = 0.01$) were associated with higher DFS probability. Other characteristics shown in Table 6 were also associated with higher DFS probability, but the difference did not reach statistical significance, likely due to the low number and heterogeneity of the patients.

Acute lymphoblastic leukemia (ALL)

One hundred and ninety two patients with ALL underwent UD BMT. The median interval between search activation and transplant was 6 months (range 1-27).

Altogether 79/192 patients died of TRM. Actuarial 12-month TRM was 52% (CI 42-58). Leukemia relapse occurred in 38 patients at a median of 6 months (range 2-25) after BMT. Three-year DFS from time of transplant was 33% (CI). In univariate analysis early phase (1st and 2nd CR) at BMT ($p = 0.006$)

was associated with higher DFS probability (37% vs 21%). Other characteristics, including year of transplant and recipient age, made no difference in DFS.

Acute myeloblastic leukemia (AML) and myelodysplasia (MDS)

Sixty patients with AML and 68 with MDS underwent UD BMT. The median interval between search and transplant was 6 months (range 2-31).

Altogether 73/148 patients died of TRM. Actuarial 12-month TRM was 54% (CI 47-65). Disease progression occurred in 30 patients at a median of 4 months after BMT (1-38). Actuarial 3 year relapse rate was 39% CI 30-56).

Three year DFS was 31% (CI 19-43) for 70 patients \leq 18 years of age while it was 23% (11-34) for 78 patients $>$ 18 years of age ($p=ns$).

Non malignant disorders

Before 1998 only few patients with severe aplastic anemia, mostly in advanced phase underwent UD BMT.

The results of these patients were disappointing. However, preliminary data of a prospective multicentric trial designed for patients in an earlier phase seem encouraging.

Eighty three patients with inborn errors underwent UD BMT. Underlying diagnosis is reported in Table 7. The median interval between search activation and transplant for these patients was 6 months (range 1-38). Altogether 27 out of 83 patients died of TRM. Actuarial 12-month TRM was 30% (CI 21-42). Graft failure and recurrence of the underlying disease occurred in 13 patients at a median of 1 month (1-12) after BMT. Three year DFS was 54% (CI).

Discussion

The reported experience is encouraging and shows that a great deal of people are, indeed, willing to donate their bone marrow in Italy and around the world. This has been made possible thanks to good cooperation between volunteers and medical and non-medical staff.

Our data show that an acceptable donor was found for 66% of the patients. This is approximately 50% higher than what we reported in 1996.⁵ The recruitment of more than 100,000 Italian donors over the last 36 months will probably further increase the number of patients who will find an UD in the IBM-DR.

In our study the average time from search activation to transplant was 6 months for diseases other than CML. In CML the median interval between search activation and transplant was 14 months. Actuarial 12-month TRM was 68% in patients grafted between

Table 7. Diagnosis of 83 patients with inborn errors undergoing UD BMT.

Diagnosis	No. of pts	ADF	AWD	Dead
SCID	19	15	-	4
Thalassemia	18	10	4	4
Fanconi anaemia	13	3	-	10
Storage disorders	9	7	-	2
HLH	8	4	-	4
Wiskott Aldrich S.	8	6	-	2
Osteopetrosis	4	2	1	1
Shwachman S.	1	1	-	-
Chediak Higashi	1	1	-	-
Kostman	1	-	-	1
Dyserythropoietic anaemia	1	-	-	1
Total	83	49	5	29

Abbreviations: ADF=alive disease free; AWD=alive with disease; SCID=severe immunodeficiency; HLH=hemolympohistiocytosis

1979 and 1992 and 44% for patients grafted between January 1993 and December 1999. The long amount of time required for the search, and the salvage chemotherapy before transplant are likely the main reasons for the high TRM rate in patients with acute leukemia. This suggests that early transplant and a decrease in early TRM could substantially change the outcome of these patients.

Most reports claim that disease stage and chronic phase duration of CML patients are major determinants of outcome.^{13,14} In the present report very few patients received transplant within one year of diagnosis and 106 out of 251 were no longer in first chronic phase at the time of BMT. The high risk of TRM as well the chance of severe GvHD were causes of concern for UD BMT early in the course of the disease. Moreover, most patients were part of a prospective study aimed at assessing the efficacy of 1 year IFN- α administration.

It must be noted that every year 15-20% of patients progress to blastic crisis and are denied the transplant option. Moreover, the decreased risk of TRM observed in patients grafted after 1992 produced a significant improvement in prognosis of patients receiving BMT from an "extensively" matched UD after a TBI-containing regimen.¹⁵ This is why the search for an UD for CML patients below 45 years of age should be activated at diagnosis. An initial trial of IFN- α may be appropriate for these patients as well as for those over 45 years old. Allogeneic transplant early in the course of disease may be the approach of choice for patients below 45 years of age with an available donor.

The results we obtained in patients with inborn errors are similar to other series¹⁶⁻¹⁹ and confirm our previous reports.^{20,21} SCID, HLH and Wiskott-Aldrich's disease represent an absolute indication to UD BMT.

TRM is the major obstacle to the success of this procedure in patients with Fanconi's anemia and osteopetrosis. The best conditioning regimen for this disease is still to be identified. Long-term follow-up of children with storage disorders suggests that after BMT the loss of intelligence continues despite persistent engraftment and normalisation of enzymatic activity. Therefore, early diagnosis is very important if an UD BMT is to be attempted.²²

In a previous report we showed that rejection was the main problem for thalassemic patients who undergo UD BMT.²¹ The incidence of rejection seems to have decreased with the introduction of thiotepa in the conditioning regimen of more recent patients (data not shown). Indication for UD BMT is still a crucial problem in the therapeutic decision for thalassemic patients lacking a matched sibling. In these cases extensive DNA study of class II antigens is recommended and the patient should proceed to transplant only if a fully matched donor is available.

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