Influence of severe combined immunodeficiency phenotype on the outcome of HLA non-identical, T-cell–depleted bone marrow transplantation

A retrospective European survey from the European Group for Bone Marrow Transplantation and the European Society for Immunodeficiency

Yves Bertrand, MD, Paul Landais, MD, Wilhelm Friedrich, MD, Bert Gerritsen, MD, Gareth Morgan, MD, Anders Fasth, MD, Marina Cavazzana-Calvo, MD, Fulvio Porta, MD, Andrew Cant, MD, Theresa Espanol, MD, Susannah Müller, MD, Paul Veys, MD, Jack Vossen, MD, Elie Haddad, MD, and Alain Fischer, MD

We analyzed the outcomes of 214 HLA non-identical T-cell–depleted bone marrow transplantations (BMTs), performed in 178 consecutive patients for treatment of severe combined immunodeficiencies (SCID). Patients were treated in 18 European centers between 1981 and March 1995. SCID variants, that is, absence of T and B lymphocytes (B–) or absence of T cells with presence of B lymphocytes (B+) were found to have a major influence on outcome. The disease-free survival was significantly better for patients with B+ SCID (60%) as compared with patients with B– SCID (35%) (P = .002), with a median follow-up of 57 months and 52 months, respectively. Other factors associated with a poor prognosis were the presence of a lung infection before BMT (odds ratio = 2.47 [1.99-2.94]) and the use of monoclonal antibodies for T-cell depletion of the graft (odds ratio = 1.67 [1.18-2.15]). Additional factors influencing outcome were age at BMT (<6 months) and period during which BMT was performed. Better results were achieved after 1991. Reduced survival of patients with B– SCID was associated with a higher incidence of early deaths from infection, a diminished rate of marrow engraftment, a trend to a higher incidence of chronic graft-versus-host disease, and slower kinetics of T/B immune function development. In both groups of patients, the use of busulfan (8 mg/kg total dose) and cyclophosphamide (200 mg/kg total dose) as a conditioning regimen provided the best cure rate (74% for patients with B+ SCID and 43% for patients with B– SCID, respectively), although results were not statistically significantly different from other regimens. This retrospective analysis should lead to the design of adapted measures to the performance of HLA non-identical BMT in patients with distinct SCID conditions. (J Pediatr 1999;134:740-8)

From Unité d'Immunologie et d'Hématologie Pédiatriques, Département de Pédiatrie, Hôpital Necker-Enfants Malades; Paris, France; Département de Statistiques Médicales, Hôpital Necker-Enfants Malades, Paris, France; Universitätskinderklinik und Poliklinik, Ulm, Germany; Academisch Ziekenhuis Leiden, Paediatrics, Leiden, The Netherlands; Department of Immunology and Infectious Diseases, The Hospital for Children, London, United Kingdom; Department of Pediatrics, Sahlgrenska University Hospital/East, Göteborg, Sweden; Department of Pediatrics, University of Brescia, Brescia, Italy; Department of Paediatric Immunology, Newcastle General Hospital, Newcastle, United Kingdom; and Hospital General, Immunologia, Barcelona, Spain.

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Reprint requests: A. Fischer. Unité d'Immunologie et d'Hématologie Pédiatriques, Département de Pédiatrie, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France.

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Severe combined immunodeficiencies are a group of congenital disorders characterized by severe impairment of both cellular and humoral immunity, leading to death at a young age. Human SCID comprises a group of genotypically and phenotypically heterogeneous conditions as described on the basis of genetic and immunologic

BMT	Bone marrow transplantation
GVHD	Graft-versus-host disease
NK	Natural killer
SCID	Severe combined immunodeficiencies

criteria.[1] Phenotypically, besides adenosine deaminase deficiency, 2 major forms of SCID have been identified: absence of both T- and B-lymphocyte differentiation (B– SCID) and the more common SCID phenotype characterized by selective blockade of T-cell and usually natural killer cell differentiation with presence of B cells (B+ SCID), which is either X-linked or autosomally recessive inherited.[2]

Patients with SCID have been cured by HLA identical bone marrow transplantation since 1968,[3] and since 1981, by HLA haplo-identical T-cell–depleted BMT[4] and by BMT from matched unrelated donors.[5] The results of HLA geno-identical BMT in SCID are good with an expected cure rate >95% in the last decade.[6] However, HLA non-identical T-cell–depleted BMTs are more frequently associated with failure of engraftment, graft-versus-host disease, or incomplete immune reconstitution. Therefore the survival rate is ~60% for recipients of haplo-identical T-cell–depleted marrow.[7-11]

A previous analysis of patients with SCID transplanted in Europe did not show any differences according to variant of the disorder in the probability of survival after either HLA matched or mismatched BMT.[6] The aim of this retrospective study was to compare the results of HLA non-identical T-cell–depleted BMT performed as treatment for B– and B+ SCID in Europe since 1981 up to 1995 and collected in the database of the European Group for Bone Marrow Transplantation (EBMT) and the European Society for Immunodeficiency (ESID).

PATIENTS AND METHODS

Between 1981 and March 1995, 178 patients with B– or B+ SCID received HLA non-identical T-cell–depleted BMT in 18 cooperating centers in Europe. Data on all BMTs performed during this period were collected from members of the EBMT/ESID. The analysis was performed on data available up to December 1, 1995, giving a minimum follow-up period of 6 months and a maximum of 14 years. B+ SCID was defined as blood T-cell counts (excluding maternal T cells) <250/μL and B-cell counts >50/μL. B– SCID was defined as T-cell counts (excluding maternal T cells) <250/μL and B-cell counts <50/μL. All patients had normal adenosine deaminase enzymatic activity.

Among the 178 patients, 122 had B+ SCID and 56 had B– SCID; there were 134 male patients (102 and 32 with B+ and B– SCID, respectively) and 44 female patients (20 and 24 with B+ and B– SCID, respectively). The median age at transplantation was 7 months for patients with B+ SCID and 6.5 months for those with B– SCID. The 122 pa-

Table I. Clinical characteristics of patients with B+ and B– SCID

	B+ SCID group (n = 122)	B– SCID group (n = 56)	*P* value
No. of transplants	146	68	
Sex M/F	102/20	32/24	<.005
Age at BMT* (median)	7 mo	6.5 mo	NS
<6 mo	41 (33.5%)	21 (37.5%)	
6 to 12 mo	51 (42%)	26 (46.5%)	
>12 mo	30 (24.5%)	9 (16%)	
Year of BMT*			NS
1982-1987	40 (33%)	15 (26.5%)	
1988-1991	38 (31%)	24 (43%)	
1992-1995	44 (36%)	17 (30.5%)	
Pulmonary infection* before BMT	47 (38.5%)	20 (36%)	NS

NS, Not significant.
*Last BMT.

Table II. Transplant-related variables in B+ and B– SCID patients

	B+ SCID group (n = 122)	B– SCID group (n = 56)
Sex donor M/F (%)	74/48	25/31
Donor F/recipient M (%)	30	32
HLA compatibility*		
1 Ag mismatch (%)	8	9
2 Ag mismatch (%)	24	26
3 Ag mismatch (%)	68	65
T-cell depletion (%)		
Erythrocyte rosettes (%)	31	30.5
Lectin + rosettes (%)	19	12.5
mAb (%)	40	46.5
Other or unknown (%)	10.5	10.5
Conditioning regimen (%)	66	75
Conditioning regimen (%)†	70	76
Acute GVHD >II (%)	12	18
Chronic GVHD (%)	32	46

Ag, Antigen; *mAb,* monoclonal antibody.
*For 2 patients in each group HLA compatibility was unknown.
†Last BMT.

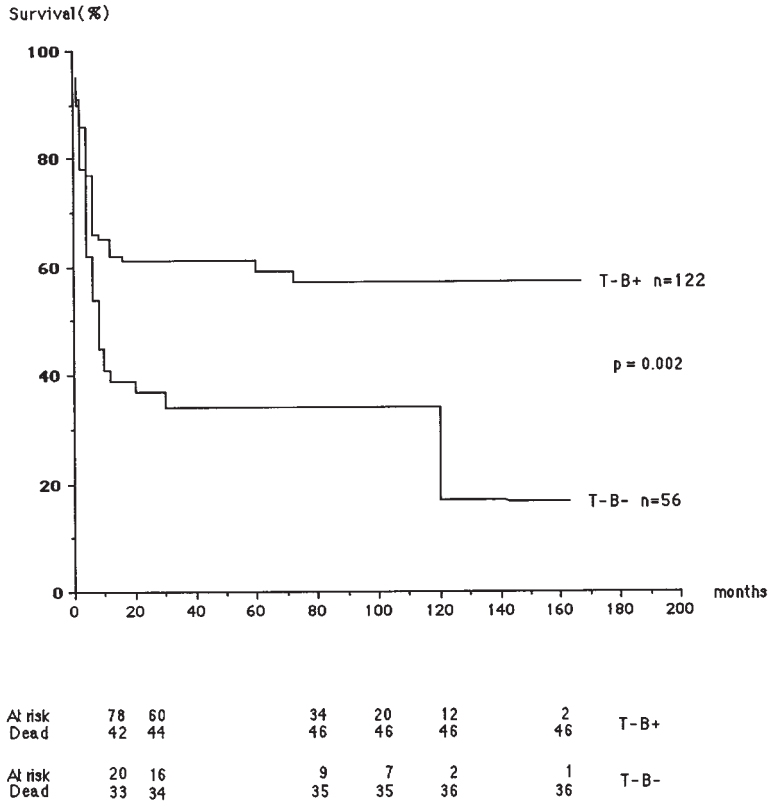

Fig 1. **A,** Cumulative probability of survival with engraftment in patients with B+ SCID versus those with B– SCID treated with HLA non-identical T-cell–depleted BMT (60% vs 35%, *P* = .002).

Table III. Factors influencing the outcome of patients with B+ and B– SCID

	Patients with B+ SCID alive with engraftment		Patients with B– SCID alive with engraftment		Multivariate analysis
	%	*P* value	%	*P* value	
Pulmonary infection +	38	.001	15	.005	OR = 2.47
Pulmonary infection –	74.5		46		
HLA compatibility		NS		NS	
1 Ag disparity	77		40		
2 Ag disparity	68		38.5		
3 Ag disparity	56.5		34		
Sex (D/R)					
F/M	54	NS	33	NS	
Other	62		36.5		
T-cell depletion					
E-rosetting/lectin	64	NS	50	.002	OR = 1.67
Monoclonal antibody	57		19		
Acute GVHD					
>Grade II	43	.07	10	.09	
≤Grade II	77		54		
Chronic GVHD					
Limited	90		72		
Severe	44		0		

Ag, Antigen; *OR,* odds ratio.

tients with B+ SCID received a total of 146 BMTs, and the 56 patients with B– SCID received a total of 68 BMTs. The clinical findings at BMT are given in Table I for each group of patients.

The compatibility of HLA antigens between donor and recipient was determined by HLA A, B, DR, DQ typing. All donors and recipients were related. The transplant-related variables are reported in Table II.

Thirty-seven patients with B+ SCID received BMT without a preceding conditioning regimen. All others were pretreated: 14 with cyclophosphamide (with or without antithymocyte globulin), 6 with busulfan only (8 or 16 mg/kg), 43 with busulfan (8 mg/kg) plus cyclophosphamide (200 mg/kg), 19 with busulfan (16 mg/kg) plus cyclophosphamide (200 mg/kg), and 3 with other or miscellaneous drugs. Thirteen patients with B– SCID received BMT without a preceding conditioning regimen. Cyclophosphamide was given to 4 patients, busulfan (16 mg/kg) to 1, busulfan (8 mg/kg) plus cyclophosphamide (200 mg/kg) to 21, busulfan (16 mg/kg) plus cyclophosphamide (200 mg/kg) to 9, and other or miscellaneous drugs to 8. All HLA non-identical BMTs were T-cell–depleted for prevention of GVHD.[12] GVHD was scored according to standard criteria.[13] Chimerism was studied by karyotyping, HLA typing, fluorescence in situ hybridization for the Y chromosome in sex mismatch transplants, and restriction fragment length polymorphism with minisatellite probes[14] or microsatellite genotyping. Lymphocyte populations were identified by immunofluorescence staining with T- and B-cell–specific monoclonal antibodies. Mitogen, antigen, and allogeneic cell-induced lymphocyte proliferations and serum immunoglobulin levels were analyzed by standard methods.[15]

Survival analysis was carried out by the product-limit method and comparisons of survival distribution by the log-rank test. Survival in each group of

patients was assessed by stratified log-rank test. Differences between distributions were analyzed by using the χ^2 test. Variables affecting the success of the graft were sought by means of a Cox proportional hazards model.[16]

RESULTS

Evidence of Better Prognosis for Patients with B+ SCID

As of December 1, 1995, 73 of 122 patients with B+ SCID and 20 of 56 patients with B– SCID were alive with T-cell engraftment, after T-cell–depleted non-identical BMT with a median follow-up of 57 months (range, 6 to 162 months) and 52 months (range, 6 to 161 months), respectively. Two additional patients with B+ SCID were alive and well after receiving a second BMT with a matched unrelated donor. The survival with T-cell engraftment/function was significantly better for patients with B+ SCID (60%) than for those with B– SCID (35%) (P = .002) (Fig 1, *A*). This better survival of patients with B+ SCID was not apparent in a previous analysis of patients who received transplants in European centers up to 1989.[6] There were no differences between the 2 groups of patients with regard to year of transplantation, age at transplantation, occurrence of lung infection before BMT (Table I), center repartition, factors potentially involved in BMT outcome (see below), transplant variables (ie, use of a conditioning regimen, method of T-cell depletion, sex combination between donor and recipient, and degree of HLA incompatibility) (Table II).

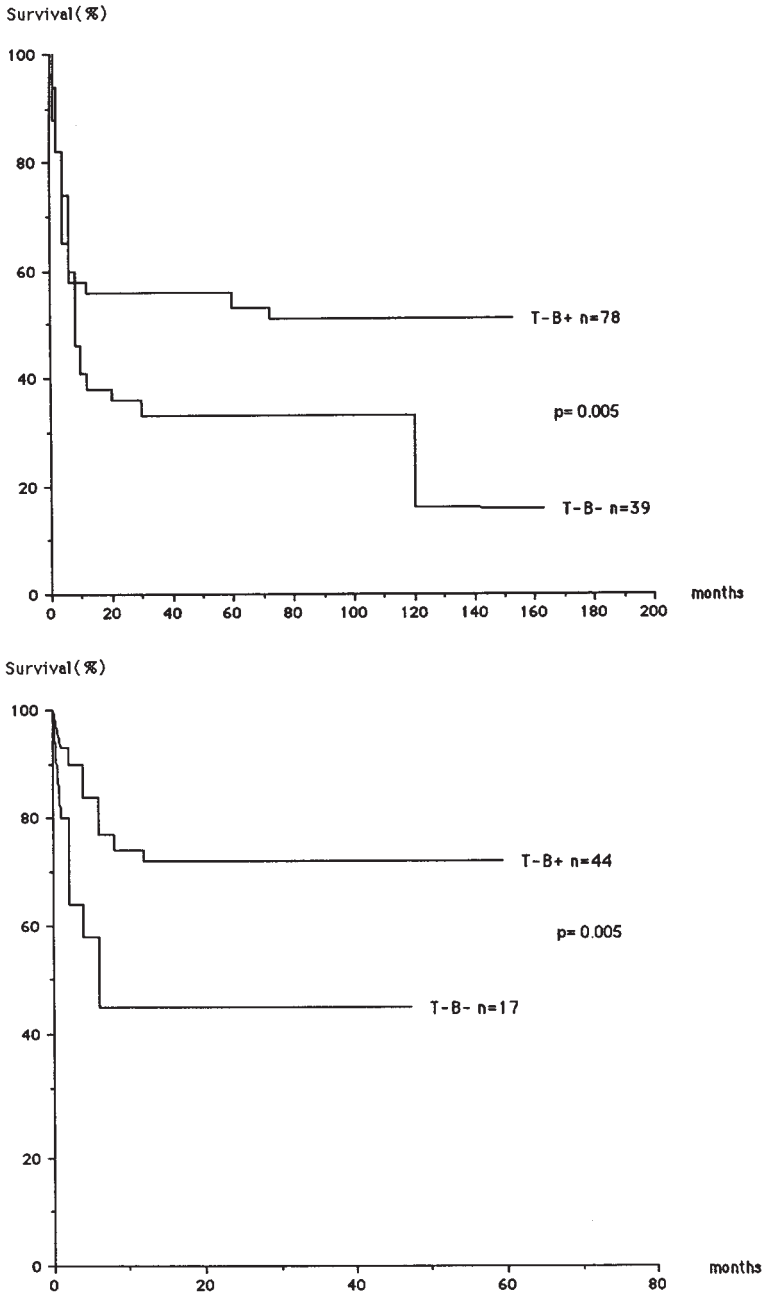

Fig 1. *Continued from previous page.* **B,** Cumulative probability of survival with engraftment in patients with B+ SCID versus those with B– SCID treated with HLA non-identical T-cell–depleted BMT according to date of transplantation (upper graph, before 1992; lower graph, 1992 or later).

Factors Influencing Outcome

The period during which BMT was performed had a significant effect on the outcome of the BMT: before as well as after 1991 the cure rate of patients with B+ SCID was significantly higher than that of patients with B– SCID (P = .005). For patients with B+ SCID, the survival increased from 52% before 1991 to 72% after 1991; for those with B– SCID, only 3 of 15 (20%) BMTs were successful before 1988 compared with 8 of 17 (47%) BMTs after 1991 (Fig 1, *B*).

Age at BMT also had a significant impact on survival with engraftment for patients with B+ SCID (73% <6 months of age vs 53% >6 months of age) (stratified log-rank, P < .05), but not for patients with B– SCID (42% vs 31%) (stratified log-rank, NS) (Fig 2). Whatever the age at BMT, the results were significantly better for patients with B+ SCID than for those with B– SCID (P = .001). The only pretransplantation clinical manifestation found to influence the outcome of HLA nonidentical BMT in both groups was

Table IV. Causes of deaths

	B+ SCID group (n = 122)	B– SCID group (n = 56)
Alive	73*	20
Early deaths <6 mo	34	24
Infections	28	21
GVHD	3	1
BLPS	2	
Other	1	2
Late deaths >6 mo	12	12
GVHD	7	7
Infections	3	4
BLPS	1	
Other	1	1

BLPS, B-cell lymphoproliferative syndrome.
*Two patients are alive after a second BMT from a matched, unrelated donor; 1 patient is lost to follow-up.

Table V. Effect of conditioning regimen on engraftment

	B+ SCID group		B– SCID group		
	No.	Engraftment (%)	No.	Engraftment (%)	*P* value
All transplants	146	69	68	59	NS
All CR	97	69	52	65	NS
No CR	49	69	16	43.5	<.05

All BMT attempts are considered.
CR, Conditioning regimen.

lung infection. The outcome was always better for patients with B+ SCID ($P < .001$) (Table III). The role of primary engraftment of maternal T cells could not be analyzed because of the restricted number of documented cases available. The modality of T-cell depletion did not affect engraftment for the B+ SCID group. However, it had a significant impact on the cure rate in the B– SCID group (Table III). Multiparametric analysis showed that disease diagnosis (ie, B+ vs B– subtype of SCID) had a major impact on survival (odds ratio = 2.24 [1.77-2.71]). After stratification between B+ and B– SCID, 2 other significant factors were found: the presence of a lung infection before BMT (OR = 2.47 [1.99-2.94]) and the modality of T-cell depletion (OR = 1.67 [1.18-2.15]) (Table III).

Causes of Deaths

Deaths in recipients of HLA nonidentical T-cell–depleted BMT were mainly related to infectious complications; the major causes of these complications were primary graft failure and lung infection, mostly of viral origin (often present before BMT). The rate of infectious deaths after the first BMT was not significantly higher in the patients who received a pretransplant conditioning regimen (data not shown). Patients with B– SCID had a higher incidence of early deaths (ie, within the first 6 months after BMT) and late deaths as compared with the B+ group ($P < .05$ and $P < .01$, respectively) (Table IV).

Factors Influencing Distinct Outcomes of Patients with B+ and B– SCID After HLA Nonidentical T-cell–depleted BMT

ENGRAFTMENT AND INFLUENCE ON OUTCOME (TABLE V). Overall rate of engraftment, considering all transplant attempts, was not different between the B+ SCID group and the B– SCID group. Within the B– SCID group, the engraftment rate was significantly higher in patients treated with busulfan and cyclophosphamide than for those who were not pretreated with a conditioning regimen ($P < .05$). Survival with engraftment was significantly better for the B+ SCID group than for the B– SCID group (Table VI), regardless of whether pretransplant chemotherapy was used.

The use of anti-LFA1 monoclonal antibody did not improve engraftment and survival among children with B+ SCID. However, for the group of patients with B– SCID, there was a trend for better engraftment because a 65% engraftment rate was observed for the population treated with anti-LFA1 antibody, and a 100% engraftment rate was observed for the 7 patients who received both busulfan (8 mg/kg total dose) and cyclophosphamide as a conditioning regimen, as well as anti-LFA1 antibody (data not shown). The limited number of patients (n = 43) led to a lack of power.

Survival with successful T-cell engraftment was documented after the first BMT in 61 of 122 children with B+ SCID. Of 61 patients with unsuccessful grafts, 38 died, 2 received matched unrelated BMT, 1 was lost to follow-up, and 20 patients received a second haplo-identical T-cell–depleted BMT (10 of which were successful). Of the 20 patients who received a second BMT, 6 died and 4 received a third BMT; of those who received a third BMT, 2 had engraftment and survived

(Table VII). In the group of patients with B– SCID, 17 patients engrafted and survived after the first BMT (30%); 28 children died after the first attempt, and 11 patients were given a second transplant, which resulted in sustained engraftment in 2 patients only; 8 patients died and 1 patient was subsequently transplanted, the third BMT being successful (Table VII).

GVHD. About half of patients at risk in both groups had acute GVHD; the frequency of grade III or IV acute GVHD is shown in Table II. Influence of acute GVHD on outcome is shown in Table III. Severe acute GVHD had a very poor prognosis in the B– SCID group. Chronic GVHD frequency is indicated in Table II. The prognosis for extensive chronic GVHD was poor, with survival rates of 44% and 0% in the B+ SCID and B– SCID groups, respectively (Table III).

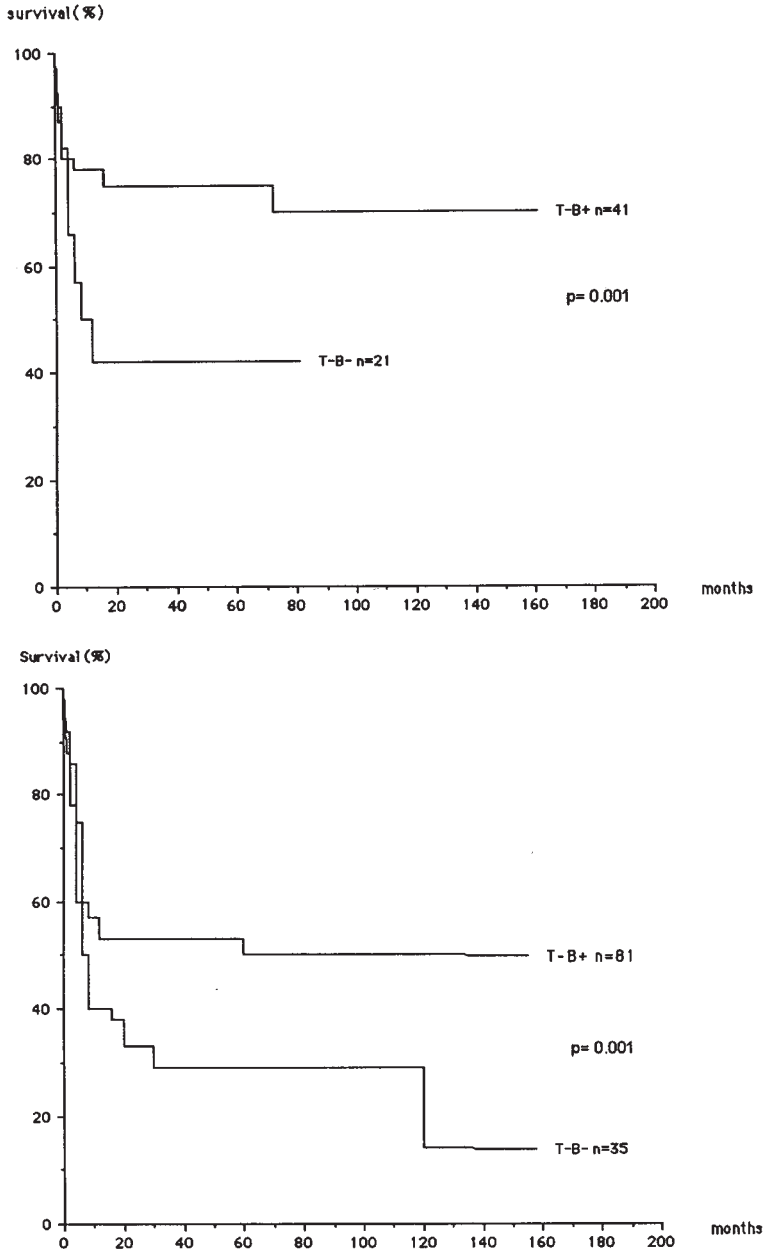

Fig 2. Cumulative probability of survival with engraftment in patients with B+ SCID versus those with B– SCID treated with HLA non-identical T-cell–depleted BMT according to age at transplantation (upper graph, <6 months; lower graph ≥6 months).

DISCUSSION

In this retrospective study we found that the results of HLA non-identical T-cell–depleted BMT were significantly better for the group of patients with B+ SCID than for the group of patients with B– SCID. The 2 populations of patients were comparable for age at BMT, clinical status before BMT (including frequency of lung infection associated with poor prognosis), period during which BMT was performed, HLA incompatibility, conditioning regimen, modalities of T-cell depletion, donor/recipient sex compatibility, center repartition, and supportive care. Previous unicentric and multicenter surveys, including a previous European study, did not detect a difference,[6,8,11,17] most likely because of insufficient study group size.

Reduced survival of patients with B– SCID appeared to be associated with a diminished rate of engraftment (particularly in the absence of a conditioning regimen), a trend to a higher frequency of chronic GVHD, increased severity of GVHD, a slower recovery of T/B immune function as demonstrated in another study,[12] and a lower rate of full T/B cell function.[12] These findings are certainly intricate, as for instance, engraftment of T-cell–depleted marrow in patients with B– SCID required the use of a conditioning regimen, a setting known to increase the risk of GVHD and associated with delayed immune function development. Nevertheless, it was striking to observe that the frequency of both early deaths (presumably related to failure of engraftment, acute GVHD, and slow pace of immune function development) and late deaths (related to chronic GVHD and poor quality of immune function) were equally increased in the B– SCID

Table VI. Effect of conditioning regimen on engraftment and survival

	B+ SCID group			B– SCID group		
	No.	Engraftment (%)	Alive (%)	No.	Engraftment (%)	Alive (%)
All patients	122	80.5	60	56	69.5	35.5
No CR	37	83.5	54	13	54	23
All CR	85	79	62	43	74	39.5
Bu 8 Cy200	43	93	74	21	86	43
Other CR	42	64	50	22	63	36

See text for *P* values.
CR, Conditioning regimen; *Bu 8 Cy200,* busulfan, 8 mg/kg, and cyclophosphamide, 200 mg/kg.

Table VII. Outcome of second and third BMT

CR Ist BMT	CR 2nd BMT	CR 3rd BMT	Follow-up
B+ SCID group			
No CR	No CR		Early death
No CR	No CR		Early death
No CR	No CR	No CR	Early death
No CR	No CR		Alive and well
No CR	No CR		Alive and well
No CR	Bu-Cy		Alive and well
No CR	Bu-Cy		Early death
No CR	Bu-Cy		Alive and well
No CR	Bu-Cy		Alive and well
No CR	Cy		Alive and well
Bu-Cy	No CR	VP 16 + Rx	Early death
Bu-Cy	No CR		Alive and well
Bu-Cy	No CR	No CR	Alive and well
Bu-Cy	No CR		Early death
Bu	Bu-Cy		Alive and well
Bu	Bu-Cy		Early death
Bu	Cy		Late death
Cy	Bu-Cy		Alive and well
Cy	Bu		Alive and well
Cy-etoposide	Cy	Bu-Cy	Alive and well
B– SCID group			
No CR	No CR		Early death
No CR	Bu-Cy		Alive and well
No CR	Bu-Cy		Late death (9 y)
No CR	Bu		Early death
No CR	Bu-Cy	No CR	Alive and well
Bu-Cy	No CR		Early death
Bu-Cy	No CR		Early death
Bu-Cy	No CR		Early death
Bu-Cy	Cy-Thiotepa		Early death
Cy	Cy		Early death
Cy	Bu-Cy		Alive and well

Cy was 200 mg/kg total dose, Bu 8 mg/kg total dose, Thiotepa 10 mg/kg total dose, and VP16 600 mg/m^2 total dose.
CR, Conditioning regimen; *Bu,* busulfan; *Cy,* cyclophosphamide.

group. This likely indicates that multiple factors account for the observed difference in prognosis.

Because no other detectable variables were found to differ, mechanisms related to SCID disease subtypes must be envisaged. Maternal T-cell engraftment, an underrecognized feature in B+ and B– SCID, has been suggested to influence engraftment and outcome.[8,11] Although this factor could not be properly assessed in this multicenter study, careful single-center analysis has not detected a higher incidence of maternal T-cell engraftment in B– SCID compared with B+ SCID.[8]

The molecular basis for most cases of B+ SCID and some cases of B– SCID is now known. B+ SCID is caused by mutation either in the γc gene, inducing defective T and NK cell differentiation in its X-linked form,[18] or in the JAK-3 gene with similar consequences.[19] In a small subset (5%) of cases of B+ SCID, molecular basis has not yet been found. Some B– SCID (6 of 14 in one study) have been found to be caused by mutations in RAG 1 or RAG 2 genes, inducing absence of TCR and immunoglobulin gene rearrangements and thereby cell death, causing lack of mature T and B cells, whereas NK cell differentiation occurs normally.[20] In a separate study it was found that cells from 7 of 11 patients with B– SCID had abnormal radiosensitivity, as also found in the B– murine SCID model, in addition to a defect in rearrangement of T-cell receptor and immunoglobulin gene

elements.[21,22] Although not identical to the murine SCID because DNA protein kinase activity is normal in these cases,[22] a large proportion of human B– SCID seems to be associated with a defect in both DNA double-strand break repair and T-cell receptor/immunoglobulin gene rearrangements. In the latter group of patients, as in patients with RAG 1/2 mutations, NK cell differentiation does occur normally. It is therefore tempting to correlate poor engraftment in patients with B– SCID to the presence of NK cells, as previously suspected (independently of SCID phenotypes).[6,9,11,23] NK cells are known to mediate marrow graft rejection in murine models, including murine models of SCID,[24,25] and could well be responsible for the poor engraftment rate of T-cell–depleted marrow in B– SCID, especially in cases characterized by extensive T-cell depletion with anti-T-cell monoclonal antibodies.[26] This finding is also in accordance with the observed better engraftment rate after use of busulfan and cyclophosphamide and possibly anti-LFA-1 antibody, which is known to profoundly inhibit NK cell activity.

One could also hypothesize that in a fraction of cases of B– SCID with a defect in DNA repair, cellular lesions caused by conditioning regimen, GVHD, and possibly infections are less well repaired, thereby favoring complications that ultimately lead to death. To test this hypothesis, it will be necessary to separately assess the outcome of patients with B– SCID who present with increased cell radiosensitivity and of patients with B– SCID without increased cell radiosensitivity (and RAG ½ mutations). If this hypothesis turns out to be correct, it would lead to further differential strategy in performing haplo-identical T-cell–depleted BMT for patients with B– SCID.

The analysis of both groups of patients also showed improved results of BMT during the past few years: this could be related to more effective treatment of infections, before and after BMT (30% of early deaths from infection before 1988 vs 14% after 1991 in the B+ SCID group), and to a more frequent use of chemotherapy for patients with B– SCID.

In conclusion, this retrospective study shows a more favorable prognosis for T-cell–depleted BMT in patients with B+ SCID as compared with those with B– SCID. The use of a conditioning regimen in the latter group of patients increased the rate of engraftment and led to a more complete immune reconstitution pattern. Further improvement of the results could include an adapted conditioning regimen to ensure complete engraftment without major toxicity. In patients with B– SCID and increased cell radiosensitivity, the administration of nontoxic blocking monoclonal antibodies to suppress cells contributing to resistance to engraftment could be beneficial together with a better prevention of GVHD with a more selective T-cell depletion.[27]

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