Bone Marrow Transplantation (2009) 44, 27–33

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ORIGINAL ARTICLE

Allogeneic hematopoietic SCT for patients with autoimmune diseases

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Allogeneic hematopoietic SCT (HSCT) has been used as treatment for single patients with autoimmune diseases (AD). To summarise currently available information, we analyzed all patients who underwent allogeneic HSCT for AD and who reported to the European Group for Blood and Marrow Transplantation (EBMT) database. Thirty-five patients receiving 38 allogeneic transplantations for various hematological and non-hematological AD were identified. Four patients had had an allogeneic HSCT for a conventional hematological indication in the past. Fifty-five per cent of the transplantation procedures led to a complete clinical response of the refractory AD and 23% to at least a partial response. The median duration of response at the last follow-up was 70.7 (15.2–130) months. Three patients relapsed at a median of 12.3 months after HSCT. Treatment-related mortality at 2 years was 22.1% (95% CI: 7.3–36.9%). Two deaths were caused by progression of AD. The probability of survival at 2 years was 70%. No single factor predicting the outcome could be identified. The retrospective nature of this study and the heterogeneous, partly incomplete data are its limitations. However, allogeneic HSCT can induce remission in patients suffering from refractory AD. These data provide the basis for carefully conducted prospective trials.
Bone Marrow Transplantation (2009) **44,** 27–33; doi:10.1038/bmt.2008.424; published online 12 January 2009
Keywords: autoimmune diseases; allogeneic; SCT

Introduction

Experimental animal data and experience stemming from patients who had received hematopoietic SCT (HSCT) for a conventional hematological indication and suffering from a concomitant autoimmune disease (AD) suggest that allogeneic HSCT can substantially alter the course of AD.[1–5] Most of the reported patients showed ongoing remission of their AD after HSCT. However, relapse of AD was reported in some rare cases.[6] In one patient with rheumatoid arthritis and concomitant myeloma, the rheumatoid arthritis relapsed despite 100% chimerism in the peripheral blood.[7] In contrast to autologous HSCT, allogeneic HSCT aims at induction of tolerance through transfer of a genetically different and presumably healthy immune system.[8]

Treatment-related morbidity and mortality associated with allogeneic HSCT have been the main impediments to trials for patients with severe AD. However, improved risk assessment and supportive care have reduced TRM in allogeneic HSCT in the recent years.[9] This and the increasingly successful experience of the European Group for Blood and Marrow Transplantation (EBMT) with autologous HSCT for AD have stimulated interest in defining the role of allogeneic HSCT for these disorders.

Patients and methods

Study design

This is a retrospective analysis of all patients reported to the EBMT data management system ProMISe who had received an allogeneic HSCT for AD. Patients transplanted for a hematological malignant disease with a concomitant AD were excluded from analysis. All centers reporting an identified patient were contacted and asked for

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Received 29 July 2008; revised 11 November 2008; accepted 17 November 2008; published online 12 January 2009

confirmation and update on the exact diagnosis, transplant procedure, complications and disease status at last follow-up using a questionnaire.

Patients characteristics

We identified 35 patients who had undergone 38 allogeneic HSCT for AD between 1984 and 2007. The patients were treated at 26 centers in 11 European countries (Appendix 1). Completed questionnaires were sent back for 21 patients. For another 12 patients, follow-up data from the ProMISe database were available. Two patients had no follow-up documented.

The median age of all 35 patients at diagnosis was 14.4 (0.1–53.4) years. Fourteen patients were female, 21 male, 18 had a hematological AD and 17 a non-hematological AD. Donors were identical siblings for 24 patients, matched unrelated donors for three, mismatched unrelated for three, mismatched related for two and syngeneic for three patients. The graft source was about equally often peripheral blood and BM, and for two patients it was cord blood. Conditioning included Cy in 22, fludarabine in 12 and TBI in five patients. Serotherapy with antithymocyte globulin was given in 13 patients. Thirteen patients were reported to have received a reduced-intensity conditioning. In all, 13 patients developed acute GVHD and 10 chronic GVHD.

Four patients had earlier received a allogeneic HSCT for a conventional hematological indication. The second HSCT was performed at a median of 61 months after the first HSCT (range 3–144 months). Three patients underwent two allogeneic HSCT for AD (patients 8, 18, 34 in Table 1). Eight patients had earlier received an autologous HSCT. The details of patients characteristics and transplantation procedures are given in Table 1.

The case of nine patients, five of whom were suffering from Evans syndrome, two from autoimmune hemolytic anemia , one from pure red cell aplasia and one from pure white cell aplasia, had been published in 2004 in an analysis of the effect of HSCT on autoimmune cytopenia.[10] Patient 3 had been included in an analysis of patients treated with HSCT for vasculitic diseases.[11]

Statistics

Discrete variables were expressed as counts (percentage) and continuous variables as medians and interquartile ranges. Frequency comparison was done by chi-square test. For data not distributed normally, the Mann–Whitney –*U* test was used. Univariate Cox regression models were used to calculate the hazard ratio for mortality, and Kaplan–Meier curves were used for graphical display. Calculated logistic regression models were used for response analysis. *P*-values less than 0.05 were considered to be significant. All statistical analyses were carried out using STATA 9.2 (Stata Corp, College Station, TX, USA).

Results

Response to treatment

At the time of transplantation, all patients had active disease refractory to standard therapy. From 38 HSCTs, nine were not evaluable for response because of missing follow-up for two patients and early TRM in seven patients (<3 months after HSCT). In the remaining 29 evaluable transplantations, complete clinical and laboratory remission could be obtained in 55% and PR in another 24%. The median duration of response at the last follow-up for the 20 patients responding partially or completely was 70.7 months (range: 15.2–130 months). Three patients (patients 3, 20 and 33 in Table 1) relapsed at a median of 12.3 months after HSCT.

All patients who received a BM graft responded at least partially. Eleven of the 12 patients who experienced acute GVHD responded to HSCT, and all 10 patients who reported with chronic GVHD responded to HSCT. No significant factor predicting response could be identified. Response was independent of the underlying disease (hematological vs non-hematological AD), age at HSCT (cut-off 20 years) and donor type (identical siblings vs unrelated donor). The use of different conditioning regimens did not appear to influence the response, nor did T-cell depletion with antithymocyte globulin. The odds ratios and the respective confidence intervals for the analyzed factors are given in Table 2.

Survival and treatment-related complications

At the time of this analysis, 61% of patients were alive. TRM was 22.1% (95% CI: 7.3–36.9%) at 2 years and 30.7% (95% CI: 13.2–48.2%) at 5 years. Death due to progression of AD was 3.2% (95% CI:0–7.3%) at 2 years and 8.7% (95% CI: 0–21.2%) at 5 years (Figure 1).

The median duration of follow-up of the 13 non-survivors was 5.2 months (interquartile range 2.1–28.4 months) and that of the 20 survivors was 67.8 months (interquartile range 28.2–86.1 months). No significant factor predicting survival could be identified.

The hazard ratios for mortality did not show any significant differences in subgroup analysis. This was analyzed for diagnosis (hematological vs non-hematological AD), age at HSCT (cut-off 20 years) and donor type (matched related vs unrelated). The two patients who had a syngeneic donor survived.

Whether conditioning was Cy based, Fludarabine based or contained antithymocyte globuline had no significant influence on survival. Three of five patients who received TBI died of TRM (infection, hemorrhage, multiorganic failure). The hazard ratios for the subgroup analyses are shown in Table 2.

Outcome after repeated allogeneic HSCT

Three patients underwent two allogeneic HSCT procedures for AD (patients 8, 18, and 34 in Table 1), two because of disease progression and one because of graft failure. Two patients are alive after a median follow-up of 42.5 months, and patient 8 died of infection.

HSCT for AD developed after HSCT for a conventional hematological indication

Four patients had earlier received an allogeneic HSCT for a conventional hematological indication (patients 6, 9, 26, and 29 in Table 1). They underwent a second HSCT for

Table 1 Patient's characteristics, transplantation procedure and outcome

Patient	*Diagnosis*	*Sex*	*Age at tx years*	*Indication for earlier allo tx*	*Conditioning*	*Donor*	*Cell origin*	*GVHD prophylaxis*	*aGVHD maximum grade*	*cGVHD*	*Response*	*Survival status*	*Cause of death*	*Follow-up months*
Non-hematologic														
1	IBD	M	0.36		Cy, BU, ATG	Id. sib.	BM	CyA	NK	NK	NK	Dead	NK	28.4
2	IBD	M	5	—	Fludarabine, R	Mud	BM	CyA	—	—	CR	Alive	—	75
3	M. Behcet	F	30	—	Cy, Thiotepa, R	Id. sib.	BM	CyA, MTX	3	Extensive	PR	Alive	—	53.2
4	M. Behcet	F	37	—	Cy, TBI	Id. sib.	PB	CyA	NA	NA	NA	Dead	Infection	0.2
5	Cryoglobulinemia	M	59	—	BU, ATG, R	Id. sib.	BM	NK	4	—	PR	Alive	—	15.2
6	PAN	M	24	Aplastic anemia	Cy, ATG, ATG	Id. sib.	PB	NK	—	Limited	CR	Alive	—	124.7
7	WG	M	21	—	NK, TBI, R	Id. sib.	PB	CyA	—	—	Progression	Alive	—	28.2
8	SLE	F	25.2	—	BU, Fludarabine, ATG, R	Id. sib.	PB	CyA, MTX	—	—	Progression	Alive	—	38.2
8	SLE	F	25.3	SLE	No conditioning	Id. sib.	PB	CyA	—	NA	NA	Dead	Infection	2.9
9	Dermatomyositis	F	28	AML	Cy, Fludarabine, R	Id. sib.	PB	NK	—	Extensive	CR	Alive	—	111.6
10	RA	F	42	—	Cyc	Syn.	PB	—	—	—	PR	Alive	—	69.7
11	RA	F	45	—	Cyc, R	Syn.	BM	—	—	—	PR	Alive	—	28
12	RA	NK	9	—	NK	Id. sib.	BM	NK	2	—	CR	Alive	—	44.8
13	MS	M	35	—	Cy, Fludarabine, R	Id. sib.	PB	NK	1	Extensive	PR	Alive	—	55.1
14	MS	M	32	—	NK	Id. sib.	PB	NK	1	—	Stable disease	Alive	—	19.3
15	Autoimmune, unspecified	M	6	—	NK	Id. sib.	BM	—	—	NA	NA	Dead	TRM	2.1
16	Autoimmune, unspecified	F	18	—	BU, Cy, ATG	Id. sib.	BM	CyA	—	—	CR	Dead	Infection	4.9
17	Autoimmune, unspecified	M	16	—	NK	Id. sib.	PB	NK	NK	NK	NK	No follow-up	—	0
Hematologic														
18	PWCA	F	20.63	—	Cy, ATG	MUD	BM	CyA, MTX	—	—	Progression	Alive	—	6.3
18	PWCA	F	21.1	PWCA	Cy	MUD	BM	CyA, MTX	3	Extensive	PR	Alive	—	5.4
19	PRCA	F	17	—	Cy, ATG	Id. sib.	BM	CyA	2	Limited	CR	Dead	Malignancy	130.4
20	Evans	M	21	—	Cy, Thiotepa, R	Id. sib.	BM	CyA, MTX	1	Extensive	CR	Dead	Progression	58.8
21	AIHA	M	2	—	BU, Cy	Id. sib.	BM	CyA, MTX	2	Limited	CR	Alive	—	3.9
22	AIHA	M	2	—	Fludarabine, ATG, R	Mismatched rel	PB	CyA	NK	NA	NA	Dead	Infection	1.4
23	ITP	F	28	—	Cy	Id. sib.	PB	CyA, MTX	—	NA	NA	Dead	Hemorrhage	0.2
24	Evans	M	11	—	Fludarabine, TBI	Mismatched rel	PB	NK	—	—	Stable disease	Dead	IPN, hemorrhage	6.2
25	AIHA	M	10	—	Cy, Fludarabine, ATG, TBI	Mismatched unrel	PB	NK	—	NA	NA	Dead	Organ failure, VOD	0.7
26	AIHA	M	8	Thalassemia	Cy, ATG	Id. sib.	PB	CyA	—	—	CR	Alive	—	112.3
27	ITP	F	35	—	Cy, Fludarabine, R	Id. sib.	PB	NK	—	—	Progression	Dead	Infection	10
28	AIHA	F	9	—	Fludarabine, ATG, TBI, TLI, R	Id. sib.	BM	CyA, MMF	1	Extensive	CR	Alive	—	85.9
29	AIHA	M	14	Thalassemia	BU, Fludarabine, ATG	MUD	BM	CyA, MTX	2	—	CR	Alive	—	124
30	Evans	M	7	—	Cy, Fludarabine, ATG, R	Mismatched unrel	CB	CyA, MMF	3	—	CR	Alive	—	36
31	Evans	M	2	—	BU, Cy, ATG	Mismatched unrel	BM	CyA, MTX	2	Limited	CR	Alive	—	85.2

Table 1 Continued

Patient	*Diagnosis*	*Sex*	*Age at tx years*	*Indication for earlier allo tx*	*Conditioning*	*Donor*	*Cell origin*	*GVHD prophylaxis*	*aGVHD maximum grade*	*cGVHD*	*Response*	*Survival status*	*Cause of death*	*Follow-up months*
32	Evans	M	14	—	Campath, Cy, BU	Id. sib.	BM	CyA, MTX	—	—	CR	Alive	—	114.3
33	AIHA	F	2	—	Cy	Id. sib.	BM	NK	—	—	PR	Dead	Progression	5.2
34	PRCA	F	32.1	—	Cy, Fludarabine	Id. sib.	PB	CyA, MTX	—	—	CR	Alive	—	2.4
34	PRCA	F	32.35	PRCA	Cy, Fludarabine	Id. sib.	PB	CyA, MTX	—	NA	CR	Alive	—	70.9
35	Hematologic, unspecified	M	3	—	NK	Syn.	CB	NK	NK	NK	NK	No follow-up	—	0

Abbreviations: AIHA = autoimmune hemolytic anemia; AML = acute myelogenous leukemia; ATG = anti-thymocyte globulin; CB = cord blood; IBD = inflammatory bowel disease; Id. sib. = identical sibling; IPN = interstitial pneumonitis; ITP = idiopathic thrombocytopenia; MMF = mycophenolate mofetil; MS = multiple sclerosis; MUD = matched unrelated donor; NA = not applicable; NK = not known; PAN = polyarteritis nodosa; PB = peripheral blood; PRCA = pure red cell aplasia; PWCA = pure white cell aplasia; R = reduced intensity conditioning; RA = rheumatoid arthritis; rel = related; Syn = syngeneic; SLE = systemic lupus erythematosus; tx = transplantation; unrel = unrelated; VOD = veno-occlusive disease; WG = Wegener's granulomatosis.

AD, which developed only after the first transplantation. For three patients, the donor was their HLA-identical sibling for both transplantations, and for one patient the two donors were HLA matched and unrelated. All patients are alive and in CR of both the AD and their hematological disease.

Discussion

In this heterogeneous group of patients with severe treatment-refractory AD, the response to allogeneic HSCT was greater than 75%. This high response rate was achieved at the expense of a TRM of 20%. In our opinion, these results are positive and encouraging, particularly considering that the patients who were included had refractory diseases and many were heavily pre-treated with various treatment modalities, including autologous HSCT. These findings are in line with experimental data and reports on allogeneic HSCT in patients with concomitant AD.[5] TRM and disease progression after HSCT illustrate the limitations of allogeneic HSCT for AD. Both are comparable to reports on allogeneic HSCT for severe refractory hematological malignancies. Admittedly, this study has severe limitations. Important data were missing and the analysis was retrospective. Moreover, the small patient numbers and the heterogeneity of the AD and the transplantation procedures might have hampered statistical analysis.

Cyclophosphamide is the preferred conditioning for allogeneic HSCT in aplastic anemia,[12] a well-defined AD. We failed to show that TBI or fludarabine-containing conditioning was superior to CY-based conditioning in our patients with various AD. Similarly, we failed to document an earlier suggested[5,13] positive influence of chronic GVHD on the outcome of allogeneic HSCT in patients with AD, even though all the patients in our study who developed chronic GVHD responded at least partially to HSCT. Reduced-intensity conditioning in our patients had no influence on the outcome. We did not have data about the chimerism status and could not test the hypothesis that remission is independent of a complete engraftment of the donor immune system. Animal models at least suggest that remission of experimental AD can be achieved after non-myeloablative conditioning with mixed chimerism.[14]

Overall, the heterogeneity of the patient population and of the data did preclude the identification of factors associated with response or mortality. This does not necessarily imply that all factors were equally important.

Of special interest are the four patients who developed an AD after having received an allogeneic HSCT for conventional hematological indications. Autoreactivity after HSCT has been reported.[15–17] Owing to the reduced morbidity and mortality of HSCT and the resulting increased long-term survival of HSCT recipients, this complication will become more important in the future. Mechanisms of autoimmunity under these conditions may be different from those of classic AD, for example, transfer of autoimmunity or homeostatic expansion of autoreactive T-cells after conditioning.[16] It is comforting to note that all patients responded to re-transplantation.

Table 2 Odds ratios for treatment response to HSCT, hazard ratios for overall mortality and for TRM

Characteristics	*Response odds ratio (95%CI)*	P	*Mortality hazard ratio (95%CI)*	P	*TRM hazard ratio (95% CI)*	P
Diagnosis: hematological AD	1.30 (0.26–6.50)	0.75	1.317 (0.417–4.170)	0.64	1.159 (0.311–4.319)	0.83
Age >20 years	4.50 (0.47–42.97)	0.19	0.393 (0.086–1.797)	0.23	0.633 (0.131–3.058)	0.57
Donor type: HLA identical siblings vs unrelated donor	0.90 (0.39–2.08)	0.81	0.942 (0.650–1.366)	0.75	1.002 (0.684–1.468)	0.99
Stem cell source: PB	0.066 (0.008–0.73)	0.02	1.939 (0.614–6.119)	0.26	0.423 (0.115–1.555)	0.20
Conditioning contained						
Cy	7.64 (0.81–72.40)	0.08	0.583 (0.172–1.946)	0.38	0.742 (0.185–2.973)	0.67
TBI	0.14 (0.01–1.77)	0.13	2.677 (0.718–9.980)	0.14	3.286 (0.809–13.341)	0.10
Fla	0.73 (0.14–3.93)	0.71	0.793 (0.173–1.946)	0.73	0.599 (0.124–2.891)	0.52
RIC	0.57 (0.09–3.83)	0.56	0.503 (0.13–1.892)	0.31	0.1859 (0.022–1.602)	0.13
ATG treatment	1.88 (0.29–11.97)	0.50	1.037 (0.300–3.583)	0.96	0.828 (0.207–3.314)	0.79
Acute GVHD	4.23 (0.75–23.93)	0.10	0.142 (0.018–1.129)	0.07	ND	

Abbreviations: AD = autoimmune disease; ATG = anti-thymocyte globulin; CI = confidence interval; Fla = fludarabine; ND = not calculated due to low event numbers; PB = peripheral blood; RIC = reduced intensity conditioning; TBI = total body irradiation.

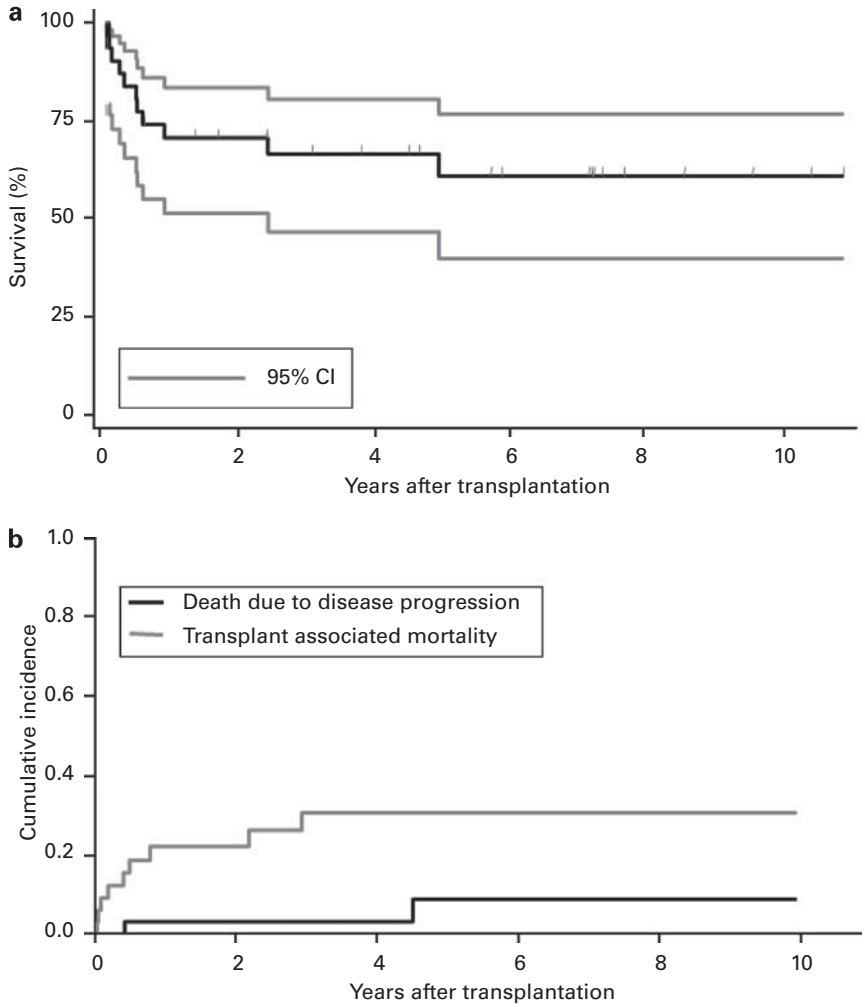

Figure 1 (**a**) Kaplan–Meier plot: survival for all patients. (**b**) Cumulative incidence of death owing to disease progression after HSCT and transplant associated mortality. CI = confidence interval.

These data suggest that allogeneic HSCT merits further exploration for selected patients with severe AD at high risk of progression. Potential candidates could be patients suffering from systemic sclerosis, multiple sclerosis or other potentially life-threatening AD with existing risk factors for an unfavorable disease outcome[18] and with presumed low-risk factors for TRM (younger age, identical sibling or well-matched unrelated donor and high Karnovsky index).

Whenever possible, patients should be treated within an established protocol.[19] The available experience with patients suffering from severe aplastic anemia and the limited data from this study suggest CY +/− antithymocyte globulin for conditioning, rather than experimental procedures.

Acknowledgements

We thank Dr Martin Stern for help with statistics and for discussion of the paper. The cooperation of all participating teams and their staff (listed in the Appendix 1), the EBMT Coordination office; Barcelona (F McDonald, E McGrath, SM Jones and EJ Mac Hale), Paris (V Chesnel, C Kenzey, C Durand and NC Gorin), London (C Ruiz de Elvira, S Hewerdine, S de Souza and N Fortin-Robertson), the Austrian Registry (H Greinix, B Lindner), the Czech Registry (K Benesova, M Trnkova), the French Registry SFGM (D Blaise, C Raffoux and Z Chir), the German Registry (H Ottinger, K Fuchs, C Müller, S Allgaier and A Müller), the Italian Registry (A Bacigalupo, R Oneto and B Bruno), the Dutch Registry (A Schattenberg, A v Biezen, M Sneets and R Brand), the Spanish Registry (J Rifon, A Cedillo, and J López), the Swiss Registry (U Schanz, H Baldomero and E Buhrfeind), the Turkish Registry (G Gurman, M Arat, F Arpaci and M Ertem) and the British Registry (C Craddock, J Cornish, K Towlson and M Wilson) is greatly appreciated. This study was supported in part by the European Leukemia Net LSH-2002-2.2.0-3, by a grant from the Swiss National Research Foundation, 3200B0-118176, the Swiss Cancer League, the Regional Cancer League and the Horton Foundation. EBMT is supported by grants from the corporate members: Amgen Europe GmbH, F Hoffmann-La Roche Ltd, Gilead Sciences UK, Miltenyl Biotec GmbH, Schering-Plough International Inc., Celegene International SARL, Genzyme, ViroPharma Europe, Chugai Sanofi-Aventis SNC, Fresenius Biotech GmbH, Gambro BCT, Bayer Schering Pharma AG, Therakos, Bristol Myers Squibb, Novartis, Pharmacon, Cephalon, Pierre Fabre Médicament, GE Healthcare, Alexion Europe, Pfizer, Biosafe SA, Merck Sharp and Dohme.

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Appendix 1

Additionally contributing EBMT centers

Hôpital Necker, Unité d'Immunologie et d'Hématologie and INSERM U 29, Paris, France.

Leiden University Hospital, BMT Centre Leiden, Leiden, The Netherlands.

University Medical Centre, Department of Haematology, Utrecht, The Netherlands.

Hotel Dieu, Department de Hematologie, Nantes, France.

Division of Stem Cell Transplantation and Immunotherapy, University Hospital Schleswig-Holstein, Kiel, Germany.

Hadassah University Hospital, Department of Bone Marrow Transplantation, Jerusalem, Israel.

Clinica di Oncoematologia Pediatrica, Dipartimento di Pediatria, Padova, Italy.

Charité-CVK, University Medicine Berlin, Pediatric Bone Marrow Transplant Service, Berlin, Germany.

Klinik/Poliklinik für Kinderheilkunde, Pädiatrische Hämatologie/Onkologie, Münster, Germany.

Unit of Hematology and Bone Marrow Transplantation, San Giovanni Rotondo, Italy.

Postgraduate Medical School, Department of Pediatrics/BMT Unit, Miskolc, Hungary.

CHRU, Service des Maladies du Sang, Angers, France.

University Hospital Gent, Haematology and Bloodbank, Gent, Belgium.

University Hospital of Palermo, Department of Hematology and Bone Marrow Transplantation, Palermo, Italy.

St László Hospital, Bone Marrow Transplantation Unit, Budapest, Hungary.

IRCCS Policlinico San Matteo, Pediatric Hematology–Oncology, Pavia, Italy.