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ORIGINAL ARTICLE

Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010

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Allogeneic hemopoietic stem cell transplantation (HSCT) is the only method currently available to cure transfusion-dependent thalassemia major that has been widely used worldwide. To verify transplantation distribution, demography, activity, policies and outcomes inside the European Group for Blood and Marrow Transplantation (EBMT), we performed a retrospective non-interventional study, extracting data from the EBMT hemoglobinopathy prospective registry database. We included 1493 consecutive patients with thalassemia major transplanted between 1 January 2000 and 31 December 2010. In total, 1359 (91%) transplants were performed on patients <18 years old, 1061 were from a human leukocyte Ag-identical sibling donor. After a median observation time of 2 years, the 2-year overall survival (OS) and event-free survival (EFS; that is, thalassemia-free survival) were $88 \pm 1\%$ and $81 \pm 1\%$, respectively. Transplantation from a human leukocyte Ag-identical sibling offered the best results, with OS and EFS of $91 \pm 1\%$ and $83 \pm 1\%$, respectively. No significant differences in survival were reported between countries. The threshold age for optimal transplant outcomes was around 14 years, with an OS of 90–96% and an EFS of 83–93% when transplants were performed before this age. Allogeneic HSCT for thalassemia is a curative approach that is employed internationally and produces excellent results.

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INTRODUCTION

More than 30 years have passed, since the first allogeneic hemopoietic stem cell transplantations (HSCT) were performed in patients with thalassemia.[1,2] After pioneering experiences in the 80s and early 90s, allogeneic transplantation remains the only widely available curative option for thalassemia major. In recent years, the indications for HSCT have been expanded, and it is now increasingly applied worldwide.[3]

The European Society for Blood and Bone Marrow Transplantation (EBMT) developed the hemoglobinopathy registry to monitor the outcomes of such patients. The registry contains relevant transplant-related information. In particular, the basic form (minimum essential data, MED-A) and the follow-up form contain patient and outcome information. With the availability of this large data set, we planned this study to verify the distribution, activity and outcomes of HSCT in the large EBMT multicenter setting.

MATERIALS AND METHODS

The hemoglobinopathy registry was established in 1995, and has since been highly active. All transplants performed before 1995 were retrospectively registered. To ensure data completeness and accuracy, the EBMT allows centers to associate with and remain associates of the registry if they have consecutive prospective patient registration and provide regular follow-up updates. The registry was created from MED-A forms provided by all consecutive patients. Centers were requested to update patient follow-up data yearly and to routinely perform audits to determine the accuracy of the data. All data were regularly registered and updated by the centers in the hemoglobinopathy registry Project Manager Internet Server (ProMISe) database (www.ebmt.org).

Study design

All patients registered in the ProMISe database of the EBMT hemoglobinopathy registry were extracted and analyzed using the ProMISe MED-A and follow-up forms (available at: www.ebmt.org). Initially, we did not exclude

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This study was conducted on behalf of the EBMT Pediatric Disease Working Party. This study was presented as oral communication at the 2011 American Society of Hematology meeting in San Diego, CA, USA and at the plenary session of annual meeting of the Italian Association of Hematology Naples 2011.
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any patient from the analyses. However, for patients who underwent more than one transplant (failure of the first transplant) only first transplant outcome was considered for event-free survival (EFS) calculation. Next, we performed a preliminary analysis of registered patients, which revealed that early activity was concentrated at a single center. Further analyses were therefore conducted on transplants performed for thalassemia major between 1 January 2000 and 31 December 2010. Data were extracted and analyzed in July 2011, thus ensuring a minimum follow-up of 6 months per case.

Definitions and outcomes

The primary end points were overall survival (OS) and EFS. OS was calculated from date of first stem cell transplantation to death from any cause. EFS was calculated as the time to death or thalassemia recurrence, whichever was first (that is, the thalassemia-free survival). Acute GvHD was graded according to the revised Glucksberg scale.[4] Chronic GvHD was graded as either limited or extended.

Patients without events were censored at the date of their last follow-up evaluation.

Statistical analysis

OS, EFS and GvHD were estimated by the product-limit method of Kaplan and Meier, and the impact of patient- and transplant-related characteristics was assessed by the log-rank test.[5] For OS deaths from any cause and for EFS additionally any secondary diagnosis of hemoglobinopathies was considered an event.

The proportions of patients with grade III or IV acute GvHD up to day 100 were given and compared using χ^2-test. Starting from day 100, the incidence of chronic GvHD (cGvHD) was estimated taking into account the competing risk of death.[5] Outcome results are reported as 2-year event probabilities ± SE.

Statistical analyses were performed with SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Approval and ethical considerations

Patients or their legal guardians signed informed consent forms before transplantation authorizing the inclusion of personal information in the EBMT database for research purposes.

The study was approved and supported by the EBMT Pediatric Disease Working Group.

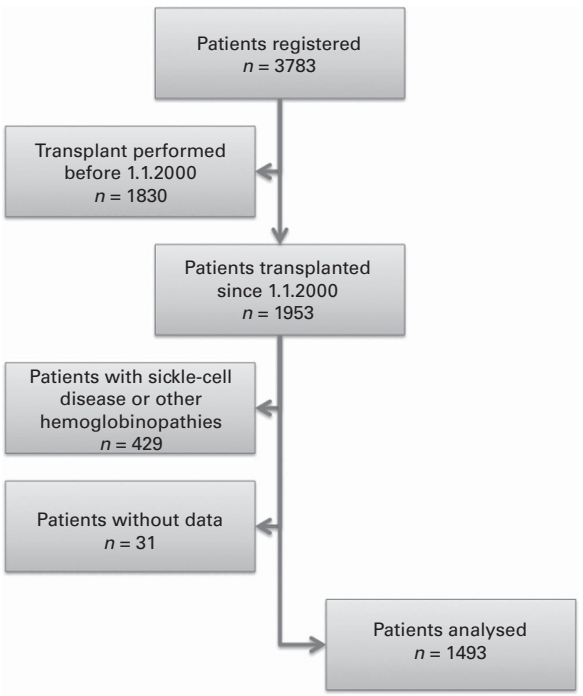


Figure 1. Study flow diagram. Patients registered in the EBMT ProMISe database and included in this report.

RESULTS

Since the start of the registry, 3783 patients affected by various hemoglobinopathies and undergoing HSCT had been reported to the registry by 31 December 2010. Data were collected from 164 EBMT centers in 30 different countries.

The experience of HSCT in the 80s and early 90s was largely in a single center. Of the 1830 globally registered transplants before 1 January 2000, 902 were performed in Pesaro between 1981 and 2000. Because the results at Pesaro have been widely reported in the literature,[6–8] we restricted the analysis to transplants performed after 1 January 2000 ($n = 1953$). Of these, 1524 patients had thalassemia major. We excluded 429 patients with sickle cell disease and other rare forms of hemoglobinopathies, and further excluded 31 transplants (2%) due to a lack of follow-up information. Accordingly, the final analysis was performed on a cohort of 1493 patients undergoing HSCT for thalassemia major between 2000 and 2010. List of contributing centers is listed in the Appendix. Figure 1 provides the flow diagram for patient inclusion.

Transplants were performed in 127 centers worldwide. The distribution was as follows: 990 in Europe (66%), 472 in Asia (32%), 26 in Africa (2%), 4 in Oceania (0.3%) and 1 in South America. Figure 2 reports the transplant distribution by country.

Of the 1493 included transplants, 1359 (91%) were performed on patients < 18 years old (median age 6.6, range 0.3–17), whereas 133 (9%) were in patients aged 18 years or older (median age 22.9, range 18–45). Data on age were missing in one case. There was a slightly increased prevalence in males than females (53% versus 47%).

Stem cells were sourced from the bone marrow in 1012 patients (67.8%), peripheral blood in 303 patients (20.3%), cord blood in 58 patients (3.9%; but, unrelated in 7 patients) and several sources (cord blood ± bone marrow ± peripheral blood) in 86 patients (5.8%). Data on the source of stem cells were missing in 34 cases (2.3%).

Concerning the HLA matching of transplant recipients, 1061 (71.1%) HSCTs were performed using HLA-identical sibling donors, 127 (8.5%) from another HLA-matched relative, 57 (3.8%) from an unmatched relative and 210 (14.1%) from a matched unrelated donor. The donor information was missing in 38 instances (2.5%).

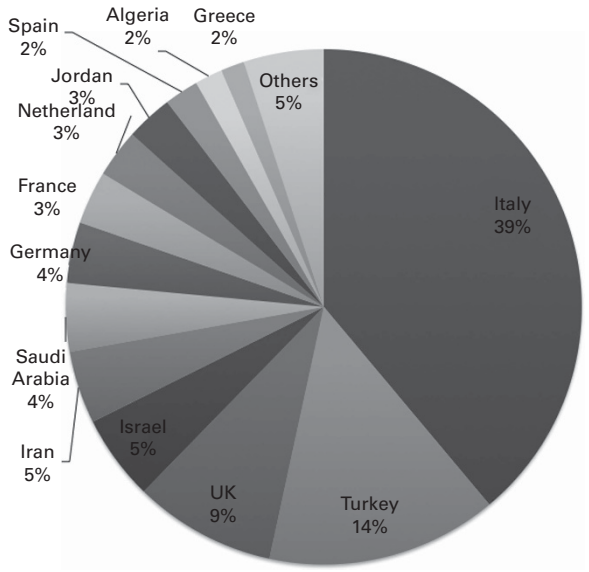
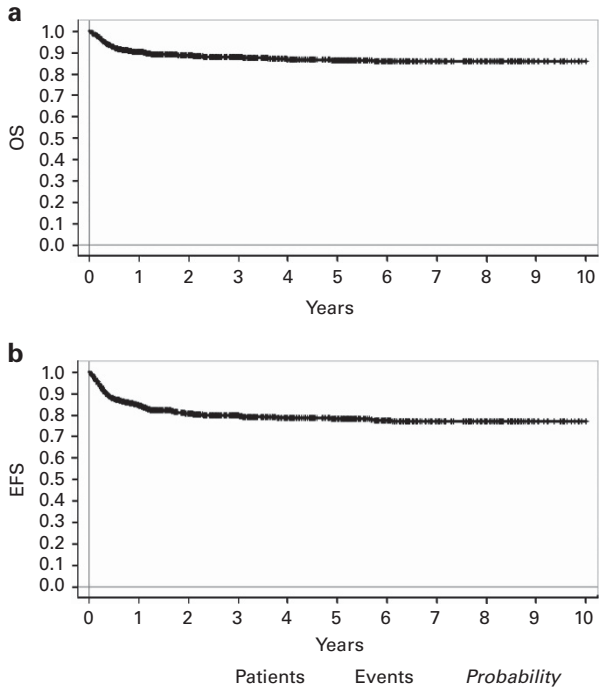
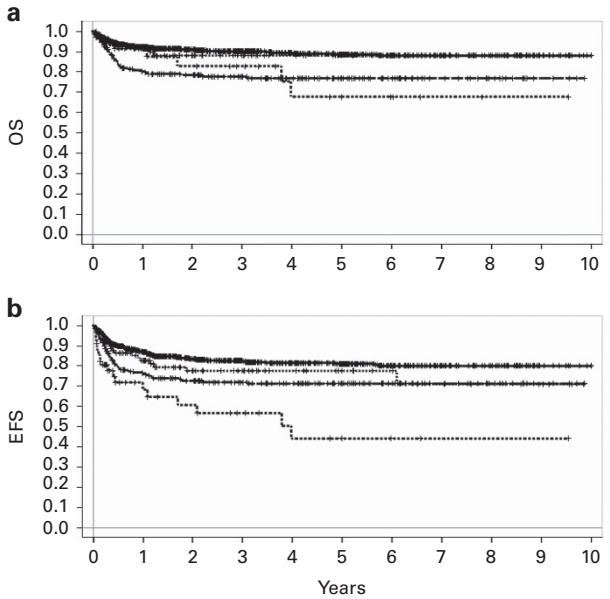


Figure 2. Country distribution of transplants in the period 2000–2010. The total number of transplant recipients was 1493. Countries that performed < 20 transplants were included in the 'other' category (Sweden = 16, Switzerland = 12, Belgium = 10, Denmark = 10, Bulgaria = 7, Austria = 6, Australia = 4, Portugal = 4, Norway = 2, Hungary = 1, Poland = 1, Argentina = 1, and Serbia and Montenegro = 1).



	Patients	Events	*Probability*
A) Overall survival	1493	154	0.88±0.01
B) EFS	1493	253	0.81±0.01

Figure 3. Survival rates for 1493 transplant recipients in the period 2000–2010. OS (**a**) and EFS (**b**) are shown.



	Patients	A) OS Events	A) OS 2-year OS	B) EFS Events	B) EFS 2-year EFS
a) MSD	1061	88	0.91±0.01	151	0.83±0.01
b) MFD	127	11	0.88±0.04	22	0.78±0.05
c) MMFD	57	8	0.68±0.11	8	0.68±0.11
d) UD	210	43	0.77±0.03	43	0.77±0.03
P-value		<0.001		<0.001	

*donor information missing in 38 cases (2.5%)

Figure 4. Transplant results by donor. OS (**a**) and EFS (**b**) by donor. MFD, matched family donor other than sibling; MMFD, mismatched family donor; MSD, matched sibling donor; UD, unrelated donor.

As shown in Figure 3, the 2-year OS and EFS were 88 ± 1% and 81 ± 1%, respectively, after a median observation period of 2 years with 250 patients having a documented follow-up >5 years. OS and EFS were 90%, 81% and 93% ($P < 0.001$), and 82%, 76% and 85% ($P = 0.003$) in patients who had received bone marrow, peripheral blood or cord blood (alone or combined), respectively.

Figure 4 summarizes the OS and EFS by donor groups, and Figure 5 shows these results by country.

The risk of developing severe (grade III–IV) acute GvHD within 100 days was 9% (108/1223) in the whole population, with a lower risk (7%; 70/901) observed in patients who had received an HLA-matched sibling donor ($P = 0.001$). In the latter group a higher risk of developing severe acute GvHD was observed in patients who had received peripheral hemopoietic stem cells (8%) compared with patients that had received bone marrow hemopoietic stem cells (3%; $P < 0.001$).

Chronic GvHD was evaluated in 1140 patients who survived with a functioning graft for >100 days. The 2-year risk of developing limited chronic or extended chronic GvHD was 15 ± 1% and 6 ± 1%, respectively. The probability of developing extended chronic GvHD was 5 ± 1% in patients who had received a graft from a matched sibling donor, 14 ± 5% in patients who had received a graft from a matched family member and 12 ± 3% in patients who had received a graft from an unrelated donor ($P = 0.004$).

No significant effect of age on acute or chronic GvHD was observed.

To explore the impact of age on OS and EFS, we performed a univariate analysis of the data for the 1060 patients who received a transplant from a matched sibling donor. Survival for pre-specified different age categories (<2 years, 2 to <5 years, 5 to <10 years, 10 to <14 years, 14 to <18 years and ⩾18 years) is shown in Figure 6, and both OS and EFS significantly decrease with increasing age ($P < 0.001$, test for trend).

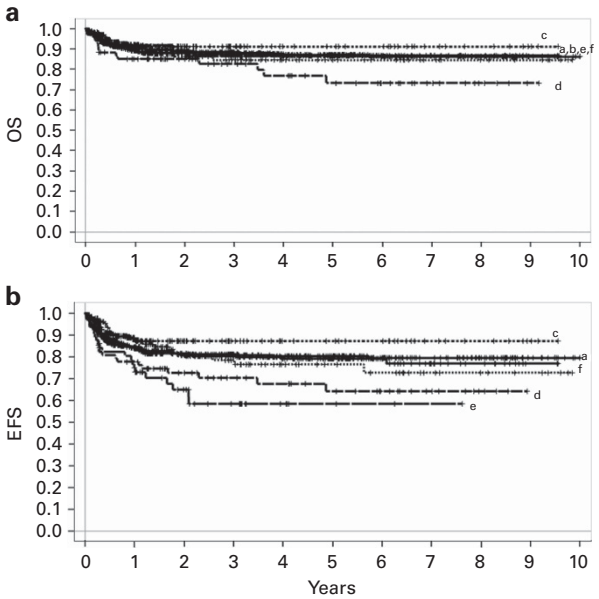
DISCUSSION

After early pioneering experience in thalassemia, allogeneic HSCT has grown in popularity to become the only curative option widely available for thalassemia major patients worldwide. The registry-collected data reported here clearly indicate that several countries, even non-industrialized countries with a low income, perform regular HSCT for thalassemia major and have outstanding results. Because the prevalence of thalassemia is high in these countries,[9] constituting a relevant social problem, the results clearly indicate a major advancement in the management of thalassemia internationally.

Furthermore, it appears that the basic message from the Pesaro group to 'transplant thalassemia patients as soon as possible' has been followed by most EBMT centers involved in transplantation for thalassemia.[7] Notably, only 133 patients aged 18 years were transplanted after the year 2000.

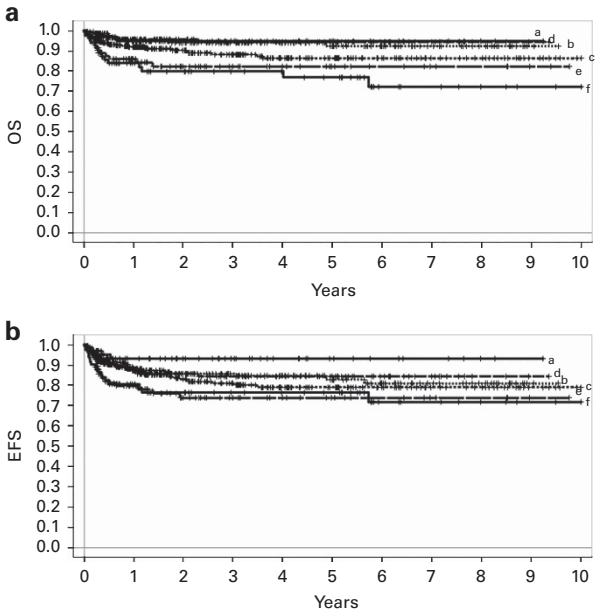
In recipients of matched sibling donor transplants, the OS and EFS (that is, thalassemia-free survival) were 91 ± 1% and 83 ± 1%, respectively. This result was markedly different compared with other donor groups (Figure 4). In this cohort, transplantation from a HLA-identical sibling donor was by far the most common procedure and had the best outcomes. The same trend was observed for both acute and chronic GvHD. Owing to the retrospective nature of the present study of registry data and the univariate method used for statistical analyses, caution should be taken when extrapolating these results to different donor groups. This is particularly important in patients who receive an unrelated donor, depending on the degree of compatibility.

Thalassemia has no time pressures when searching for a matched unrelated donor; however, this transplant type was not widely used. We identified only 210 patients (14% of the entire



	Patients	A) OS Events	A) OS 2-year OS	B) EFS Events	B) EFS 2-year EFS
a) Italy	581	55	0.89±0.02	90	0.82±0.02
b) Turkey	216	21	0.86±0.03	32	0.80±0.04
c) UK	133	10	0.91±0.03	14	0.87±0.03
d) Iran	68	14	0.85±0.04	21	0.73±0.06
e) Saudi Arabia	64	7	0.89±0.04	21	0.65±0.07
f) Others	431	47	0.88±0.02	75	0.81±0.02
P-value		0.347		<0.001	

Figure 5. Transplant results by country. OS (**a**) and EFS (**b**) are shown. Countries performing < 50 transplants were included in the 'other' category.



	Patients	A) OS Events	A) OS 2-yrs. OS	B) EFS Events	B) EFS 2-yrs. pEFS
a) < 2 years	66	3	0.95±0.03	4	0.93±0.03
b) 2-<5 years	266	13	0.94±0.02	32	0.86±0.03
c) 5-<10 years	352	33	0.90±0.02	52	0.83±0.02
d) 10-<14 years	197	8	0.96±0.02	24	0.86±0.03
e) 14-<18 years	97	14	0.82±0.04	20	0.74±0.05
f) ≥18 years	82	16	0.80±0.05	18	0.76±0.05
P-value (for trend)		<0.001		<0.001	

Figure 6. Results by age group among patients who received an HLA-identical sibling donor transplant. OS (**a**) and EFS (**b**) are shown. Age data were missing for one patient.

transplantation activity) who received an unrelated donor transplant.

The analysis of outcomes by country shows comparable 2-year OS (over 85%) with no statistically significant differences between countries. However, a slight difference was reported in EFS in our analysis.

Concerning the impact of age on outcomes, we analyzed the results of over 1000 patients who received HSCT from HLA-identical siblings. A statistically significant difference was reported in OS and EFS in different age groups, as reported in Figure 6. In this analysis, the threshold age for optimal transplant outcomes was around 14 years, with an outstanding OS of ⩾90% (range 90–96%) and EFS of ⩾83% (range 83–93%) in all age groups under this threshold. We reported continued good outcomes with thalassemia care following the pioneering experience of the Pesaro group. We are aware of only one other multicenter registry data of < 200 transplanted patients.[10]

The impact of age does not contradict the risk classification developed in the deferoxamine-only era by the Pesaro group[6] and, more recently, other groups,[10,11] indicating that clinical status, rather than age, is the most important predictor of transplant outcome.[12] The larger number of patients in this analysis could have permitted the discovery of risk factors that were otherwise undetectable in smaller or single-center analyses. However, our data also lack detailed clinical information, such as the presence of liver fibrosis or regularity of chelation therapy. Nevertheless, showing this impact of age on transplant outcomes supports the argument that thalassemia is a progressive disease resulting in tissue damage and that deterioration starts early in a patient's life, even in the era of oral chelation therapy.

Particular attention should be reserved for the results obtained in adult patients (that is, those ⩾18 years of age). As previously discussed, our experiences were limited to a specific decade (2000–2010). However, the results obtained in the 82 patients who received a matched sibling donor transplant (OS 80 ± 5% and EFS 76 ± 5%) compare favorably with those of a previous experience.[13] Direct comparison is not possible, but the observed improvement could reflect improvement in transfusion and chelation therapy and accuracy in case selection during the last decade.[3] As demonstrated by the experience at Pesaro, optimal long-life transfusion and chelation therapy, preventing anemia and iron-related tissue damage, is the key to a successful transplant.[12] The limited thalassemia recurrence rate (4%) confirms the observation of the Pesaro group that transplant-related mortality, and not thalassemia recurrence, is the major problem in adult patients.[13]

There are obvious limitations in this study based on a retrospective registry analysis. For example, patients' clinical conditions and transplantation events, such as causes of transplant-related mortality, were not detailed. Several experiences, such as those of North America and the Far-East,[14–19] were also not reported to the EBMT registry. However, the EBMT ProMISe regulations and the large number of cases reported guarantee the accuracy of the data presented. This is further demonstrated by the very limited number of missing data on survival (< 3%).

In conclusion, in the era of oral chelation therapy and in the era in which use of expensive gene therapy may be on the horizon,[20] with the large number of thalassemia patients worldwide, the outcomes, distribution, feasibility and costs of transplantation should be considered while planning resource allocation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

Appendix Contributing centers

The number of patients registered in the study period (2000–2010) is shown in parentheses.

Frankfurt, J. W. Goethe Universität, Kinderheilkunde III (3); Ankara, Gazi University, Besevle (1); Shiraz, Nemazee Hospital (16); Marseille, Hôpital Timone Enfants (4); Würzburg, Universitätsklinikum (1); Paris, Hôpital Neckar des enfants malades (3); Basel, Universitätsspital Basel (1); Leiden, University Hospital (40); Ulm, Kinderklinik Universitätsklinikum, Abt. Peds. II (4); London, Hammersmith Hospitals NHS Trust (1); Copenhagen, Rigshospitalet (10); Paris, Hôpital St. Louis (8); Leuven, University Hospital Gasthuisberg (1); Stockholm, Karolinska University Hospital, Huddinge (7); Brussels, Institut Jules Bordet, Childrens Hospital (3); London, The Royal Free Hospital (11); London, Royal Marsden Hospital (3); Rome, Università "La Sapienza", Hem Faculty 1 (1); Besancon, Hôpital Jean Minjoz and St Jacques (1); Brussels, Clinique Universitaire St Luc (4); Oslo, Rikshospitalet, Department of Medicine, The National Hospital (2); Nijmegen, University Hospital (4); Cordoba, Hospital Reina Sofia (2); Utrecht, University Hospital UMCU (1); Santander, Hospital Universitario M. de Valdecilla (1); London, Great Ormond Street Hospital (4); Pescara, Ospedale Civile (18); Nantes, Hotel Dieu, CHU Nantes (1); Leeds, St. James's University Hospital and The General Infirmary (11); Jerusalem, Hadassah University Hospital (40); Essen, Universitätsklinikum (5); Barcelona, Santa Creu i Sant Pau (3); Geneva, Hôpital Cantonal Universitaire (1); London, The London Clinic (2); Uppsala, University Hospital, Medical Clinic (3); Grenoble, CHV Grenoble (1); Clermont Ferrand, CRCTCP, CHU Estaing (3); Genova, Istituto Giannina Gaslini (4); Newcastle upon Tyne, Royal Victoria Infirmary (1); Lille, Hôpital Claude Huriez (2); Monza, Ospedale San Gerardo (1); Lund, University Hospital (4); Rome, Ospedale S. Camillo (2); Goteborg, CHECT Sahlgrenska University Hospital (2); Hannover, Medizinische Hochschule (7); Lisbon, Instituto Portugues de Oncologia (4); Torino, University Hospital (14); Zurich, Universitäts Kinderklinik (10); Berlin, Charité, Campus Virchow Klinikum (1); Napels, National Cancer Institute (3); Haifa, Rambam Medical Center (24); Sofia, Pediatric Hospital for Oncohematology and BMT (7); Belgrade, Mother+Child Health Institute (1); Ankara, GATA BMT Center, Etlik (10); Rome, Policlinico Tor Vergata, Fond. IME (146); Bristol, Royal Hospital for Sick Children (1); Riyadh, King Faisal Specialist Hospital (64); Ankara, Ihsan Dogramaci Childrens Hospital (Hacettepe) (21); Istanbul, University of Istanbul (10); Madrid, Hospital Universitario Materno Infantil Gregorio Maranon (1); Barcelona, Hospital M. Infantil, Vall d'Hebron (5); Münster, Universitätklinikum Münster (1); München, Universitätsklinikum Grosshadern, Med Klin III (1); Manchester, Royal Children's Hospital (17); Nice, Hôpital de l'Archet 1 (2); Trieste, Istituto per l'Infanzia (4); San Giovanni Rotondo, Hospital Casa Sollievo Sofferenza (1); Barcelona, Hospital General Vall d'Hebron (7); Vienna, St. Anna Kinderspital (6); Pesaro, Ospedale San Salvatore (67); Tübingen, Universitätsklinikum, Pädiatrie (2); London, St George's Hospital (2); Pavia, Policlinico IRCCS St Matteo (113); Tel Hashomer, Chaim Sheba Medical Cebter (10); Amman, King Hussein Cancer Centre (44); Klinik fuer Knochenmarktransplantation und Haematologie/Onkologie, Idar-Obestein, Germany (15); San Sebastian, Hospital Nostra Senora de Aranzazu (1); Miskolc, Postgraduate Medical School (1); Firenze, Azienda Ospedaliero Universitaria Meyer, Department of Paediatric Haematology Oncology (11); Bremen, Klinikum Bremen-Mitte, Inn. Med I (1); Hamburg, Universitätsklinikum Eppendorf (4); Antalya, Akdeniz University Medical School

(123); Ankara, University of Ankara (26); Izmir, Ege University Medical Faculty, Bornova (22); Athens, Evanghelismos Hospital (1); Brussels, University Hospital (1); Paris, Hôpital Robert Debré, Hem-Immuno (3); Teheran, Shariati Hospital (52); Düsseldorf, Universitätsklinikum (4); Valencia, Hospital Universitario La Fe (1); Lyon, Hôpital Edouard Herriot (3); Strasbourg, Hôpital Hautpierre (2); Vandoeuvre-les-Nancy, Hôpital d'Enfants (1); Randwick, Sydney Children's Hospital, Centre for Children's Cancer (2); Alger, Centre Pierre et Marie Curie (26); Glasgow, Royal Hospital for Sick Children (3); Sidney, The Children's Hospital at Westmead (2); Palma de Mallorca, Hospital Universitario Son Espases (1); Salamanca, Complejo Hospital (3); Madrid, Hospital Niño Jesus (1); Madrid, Hospital La Paz (5); Brescia, Universitá degli Studi di Brescia (2); Buenos Aires CEHT (1); Gent, University Hospital (1); Athens, Aghia Sophia Childrens Hospital (21); Petach-Tikva, Childrens Medical center (6); Rome, Rome Transplant Network¨Tor Vergata¨ University of Rome Stem Cell Transplant Unit (12); Istanbul Tip Fakultesi Iç (1); Sevilla, Hospital Universitario Virgen del Rocio (1); Sheffield, Teaching Hospitals NHS Trust, Royal Hallamshire Hospital (4); Birmingham, The Birmingham Children's Hospital (15); Bologna, Policlinico S. Orsola, Clin. Pediatrica III (7); Pisa, University of Pisa (4); Gdansk, Medical University (1); Lyon, Institut d'Hématologie et d'Oncologie Pédiatrique (9); Dresden, Universitätsklinikum Carl Gustav Carus (3); Freiburg, Universitatsklinikum, Kinderklinik (5); Cagliari, Binaghi BMT Centre (42); Cagliari, Univer Studi (70); Milan, Istituto Scientifico H.S. Raffaele (58); Catania, Pediatric Unit-Policlinico (1); London, St Mary's Hospital (58); Antalya, Medical Park Hospitals (2); Rouen, Hôpital Charles Nicolle (2); Toulouse, Hôpital Purpan (1); Strasbourg H Hautepierre (3); Bordeaux, CHU Hopitalier Pellegrin-Enfants (1).