Transplantation of Hematopoietic Stem Cells and Long Term Survival for Primary Immunodeficiencies in Europe: entering a new century, do we do better?

Running Title: Long-term survival after HSCT for PID in Europe

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Abstract

Background: Hematopoietic stem cell transplantation (HSCT) remains the only treatment for most patients with severe combined immunodeficiencies (SCID) or other primary immunodeficiencies (non-SCID PID).

Objective: To analyze long-term outcome of SCID and non-SCID PID patients from European centers treated between 1968-2005.

Methods: The product-limit method estimated cumulative survival, the log-rank test compared survival between groups. A Cox proportional-hazard model evaluated impact of independent predictors on patient survival.

Results: In SCID patients, survival with geno-identical donors (n=25) in 2000-2005 was 90%. Survival using a mismatched relative (n=96) has improved (66%), similar to that using an unrelated donor (URD) (n=46) 69%, (p=0.005). Transplantation after year 1995, a younger age, B+ phenotype, geno- and pheno-identical donors, absence of respiratory impairment, or viral infection prior to transplantation were associated with better prognosis on multivariate analysis.

For non-SCID PID, in contrast to SCID patients, we confirm that, in the 2000-2005 period, using an URD (n=124) gave a 3-year survival rate similar to a geno-identical donor (n=73), 79% for both. Survival was 76% in pheno-identical transplants (n= 23) and worse in mismatched-related donor (n=47), 46%, (p=0.016).

Conclusions: This is the largest cohort study of such patients with longest follow-up. Specific issues arise for different patient groups. B- SCID patients have worse survival than other SCID, despite improvements in each group. For non-SCID PID, survival is less good than SCID, although more conditions are now treated. Individual disease categories now need to be analysed, so that disease-specific prognosis may be better understood and best treatments planned.

Key Messages

- Transplantation for primary immunodeficiency before 6 months of age is associated with improved outcome and supports the use of newborn screening programmes to facilitate the early diagnosis of SCID.
- Prognosis following HSCT for PID is multifactorial, including molecular defect, disease status, donor, stem cell source and conditioning regimen, and it is important to now analyse the long-term outcome for disease-specific groups.

Key Words: primary immunodeficiency; severe combined immunodeficiency; Wiskott Aldrich syndrome; CD40 ligand deficiency; chronic granulomatous disease; hematopoietic stem cell transplantation

Abbreviations:

European Blood and Marrow Transplantation – EBMT

European Society for Immunodeficiency - ESID

Familial lymphohistiocytosis - FLH

Graft versus host disease - GvHD

Hematopoietic stem cell transplantation - HSCT

MMR - MisMatched Related

Primary immunodeficiencies - PID

RGI - Related Geno Identical

RPI - Related Pheno Identical

Stem Cell Transplantation for Immunodeficiencies in Europe - SCETIDE

Severe combined immunodeficiencies – SCID

URD - Unrelated Donor

Wiskott-Aldrich syndrome - WAS

Capsule Summary

This large cohort study of hematopoietic stem cell transplantation for primary immunodeficiency demonstrates improved outcome of transplantation before 6 months of age, supporting use of newborn screening programmes to facilitate the early diagnosis of SCID.

Introduction

Primary immunodeficiencies (PID) are a genetically heterogeneous group of diseases affecting distinct components of innate and acquired immunity including development and function of complement proteins, phagocytes, natural killer cells and T and B lymphocytes [1]. Severe combined immunodeficiencies (SCID) are the most severe PID, characterized by impaired T and B lymphocyte function, normally leading to death within the first year without hematopoietic stem cell transplantation (HSCT) [2]. Other T lymphocyte immunodeficiencies may present later; whilst prophylaxis improves outcome, recent studies demonstrate that long-term outlook is poor with many patients dying from infectious or inflammatory-related complications or malignancy in early adulthood [3,4]. Innate immune defects may present in infancy but prophylaxis has meant that many patients survive until early adulthood [5,6]. HSCT has been shown to be curative since 1968 and remains the only form of treatment for many patients with PID. European centers have been transplanting these patients for over 30 years; previous reports demonstrated an improvement in survival over time [7]. Over that period, HLA-tissue typing methods have been refined, new stem cell sources including umbilical cord blood have become more readily available [8] and improved methods of isolating HSC including CD34+ stem cell selection and CD3+/CD19+ depletion, developed [9]. More grafts using unrelated donors were performed. Less toxic chemotherapy conditioning regimens have been developed, improving survival in very sick patients [10]. Molecular detection of viral infection enabled pre-emptive antiviral treatment before organ damage supervenes [11]. Greater awareness of PID amongst pediatricians has lead to earlier diagnosis and referral to specialist centers. With experience of HSCT concentrated in a few centers of excellence, the chance of successful treatment with cure of disease and long-term survival has increased. Common guidelines set out by the European group for Blood and Marrow Transplantation (EBMT) and the European Society for Immunodeficiency (ESID) Inborn Errors Working Party has enabled common treatment protocols to evolve. Patient data are collected in the Stem Cell Transplantation for Immunodeficiencies in Europe (SCETIDE) registry giving data on almost 1500 patients. In this study, long-term results of HSCT in SCID and non-SCID PID, including previous cases of SCID and non-SCID PID reported in 1986, 1990 and 2003, is based on analysis of SCID and non-SCID PID patients treated in European centers between 1968-2005. Since many innovations in HSCT were introduced in the period 2000-2005, we explored whether better results were obtained compared to previous periods. The outcome of transplants from HLA (geno-) identical siblings,

phenotypically compatible non-sibling relatives (pheno-identical), unrelated donors (URD) and HLA mismatched related (MMR) donors has been assessed. The large number of cases registered in the database gives sufficient statistical power for assessment of changing trends in outcome over different periods.

Methods

Data were derived from the electronic SCETIDE database established for EBMT/ESID to register HSCT for PID [7]. All centers affiliated to the working party currently undertaking such procedures for SCID and inborn errors were enrolled. Between 1968 and December 31 2005, 37 centers collected and recorded continuous and systematic relevant data on children undergoing HSCT for SCID and other PID, gathered on the basis of a questionnaire built up and validated by the European Working Party. Each center was responsible for quality control of its own data, collated by data managers in the largest centers. Previous definitions of SCID or non-SCID PID, as recently published by the International Union of Immunological Societies [12], were used for consistency [7]. Data were transmitted to the Department of Biostatistics, Hôpital Necker Enfants Malades, Paris. Three time periods have been examined; pre-1995 as a historical period, 1995-1999 and 2000-2005. The most recent time period was analysed as a distinct time interval as many innovations in HSCT were being introduced as noted above.

Donor and recipient HLA-matching was determined by serology for the earlier patients and low resolution class I with high resolution class II molecular DNA typing in more recent patients – methods were dependent on each center's practise. Geno-identical donors were defined as HLA-identical sibling donors, pheno-identical donors as HLA-identical non-sibling family donors. Unrelated donors were mainly HLA-matched, although some were mismatched at one or two antigens. T lymphocyte depletion was performed by a number of different methods including E-rosetting with or without soybean agglutination, and in-vitro Campath 1M antibody with complement. Since the late 1990s, CD34+ positive stem cell selection rather than T lymphocyte depletion was used [9]. If given, cytoreductive chemotherapy and graft versus host disease (GvHD) prophylaxis (cyclosporine or tacrolimus) was given in accordance with the EBMT/ESID Inborn Errors Working Party treatment guidelines current at time of transplantation. Broadly, chemotherapy consisted of Busulphan-containing regimens; other chemotherapy without busulphan; ATG, Campath or OKT3 only, or no chemotherapy. Precautions to reduce the risk of infection were based on reverse isolation, including gnotobiotic isolation, although the exact mechanism employed was center dependent.

Statistical analysis:

All records available by December 31, 2005, were retained for analysis. Engraftment was evaluated in patients

alive one month after HSCT. Survival times started from date of last HSCT. A center effect was explored, and analyses were adjusted for a center effect in the multivariate analysis, comparing centers that transplanted more or less than 50 patients. Differences in observed distributions were analysed using the Chi-square test. Cumulative survival was estimated with the product-limit method. The log-rank test was used to compare survival between different groups. A Cox proportional hazard model with stepwise forward selection process was retained to evaluate impact of independent predictors (demographics, comorbidity, transplant characteristics and therapeutics before HSCT) on patient survival. Hazard ratios (HR) were provided with their 95% confidence interval. The SCETIDE database was developed using Access software (Microsoft ®Access 2000). Statistical analyses were performed using the SAS system for Windows (SAS Institute Inc, Cary, NC), and R software for multivariate analyses, using "GLM" and "Survival" libraries.

Results

Severe combined immunodeficiency patients

Data on 699 patients with SCID were collected. Details of diagnosis are shown (Table 1); over the whole time period, 49% had B+ SCID (including T-B+NK- phenotype - common gamma chain or JAK3 deficiency, and T-B+NK+ phenotype - IL7 receptor alpha deficiency), 29% had B- SCID (predominantly T-B-NK+ phenotype - recombinase activating gene (RAG) 1 or 2, or artemis deficiency) and 22% had other forms of SCID, including CD3 subunit deficiency, CD45 deficiency, and other rare molecular defects as well as genetically undefined defects. The proportions of patients presenting with each diagnosis was unchanged over time. More unrelated donors have been used as a proportion of total transplants in successive time periods, reflecting establishment of international registries, improved donor selection and harvesting procedures.

Recipient age at transplantation and number of procedures undertaken is shown (Supplementary Table E1). Median age at transplant was slightly lower in 2000-2005, but not significantly, which may reflect a trend towards earlier diagnosis and referral, or more rapid identification of suitable donors. In 2000-2005, a higher percentage of patients were transplanted > 18 months of age than previous periods, a significant increase, which may reflect improvements in supportive care or improved molecular diagnosis picking up older patients with atypical forms of SCID. Ten year survival in patients with SCID following transplantation has improved over time, although there is no difference in the two most recent time periods (Table 2, Figure 1; $p = 0.0003$). Overall, 10 year survival was better with a sibling geno-identical donor compared to other types of donor recipient compatibility (Table 2; Figure 1; $p < 0.0001$). For pheno-identical donors and URD, survival improved in the two recent periods, however the numbers per period were low and the differences did not reach significance (Supplementary Table E1). Survival using a mismatched relative has improved (Supplementary Table E1; Supplementary Figure E1; $p=0.005$) with better survival between pre-1995 and 1995-1999 periods. There was no significant difference in survival using an URD or a mismatched relative in the period 2000-2005 (Supplementary Table E1, Supplementary Figure E4). Patients transplanted before 6 months of age had better overall survival than those transplanted > 12 months old (Table 2, Supplementary Figure E2, $p=0.0008$). Survival for B+ and other forms of SCID patients remained significantly better than B- SCID (Table 2; Figure 3; $p < 0.0001$). Pre-existing respiratory impairment was associated with a worse outcome (Table 2, $p = 0,006$).

Pre-existing septicemia, liver impairment, meningeal infection, and malnutrition were also associated with a worse outcome post-HSCT. The use of chemotherapy conditioning did not significantly affect survival (chemotherapy=280 [61%]; no chemotherapy, n=399 [63%]; p =0.53) (supplementary information, supplementary Tables E2, E3). Multivariate analysis demonstrated that age at transplant, SCID phenotype, recipient/donor compatibility, pre-existing respiratory infection, protected environment, antibiotic prophylaxis and the presence or absence of T lymphocyte depletion were significantly associated with outcome (Table 2). There was a weaker significance with the presence or absence of septicemia.

Other primary immunodeficiency patients

Data on 783 patients with non-SCID PID were collected. Details of diagnosis, recipient age at transplantation, and the number of procedures undertaken are shown (Table 1, Supplementary Table E1). After 1995 the numbers and proportion of patients with inborn errors other than Wiskott-Aldrich syndrome increased. Of the T lymphocyte deficiencies, 34% had Omenn syndrome, 6% purine nucleoside phosphorylase deficiency, 32% HLA class II deficiency, 18% CD40 ligand deficiency and 10% undefined. The proportion of patients with CD40 ligand deficiency markedly increased after 1995 and the proportion of patients with other inborn errors increased in the latest time period. Of the phagocytic cell disorders, the proportion of patients with leukocyte adhesion deficiency was greater before 1995 and that of patients with chronic granulomatous disease much greater in the period 2000-2005. Of the hemophagocytic cell disorders, 62% had familial lymphohistiocytosis (FLH), 16% Chediak-Higashi syndrome, 10% Griscelli syndrome and 12% X-linked lymphoproliferative disease (the proportion of which increased in each of the time periods).

The proportion of children > 2 years being transplanted was significantly greater after 1995. The 4 year survival showed a marked improvement in 2000-2005 (Table 2; Figure 2; $p = 0.0001$), an improvement not seen in the SCID patients. Survival was better with URD than pheno-identical transplants (Table 2; Figure 2; $p < 0.0001$). Survival in the period 2000-2005 was better with an URD than a mismatched relative donor, in contrast to SCID patients (Supplementary Table E1; Supplementary Figure E5). Furthermore, survival using a geno-identical donor was almost the same as an URD, a feature not seen in the SCID group. There was a significant improvement over time in survival at 3 years for URD transplants (Supplementary Table E1; $p = 0.027$).

Univariate analysis demonstrated that 10 year survival was significantly better for patients with Wiskott-Aldrich syndrome, phagocytic and hemophagocytic disorders than for patients with T lymphocyte immunodeficiencies (WAS, n=168 [71%: 64-79%]; phagocytic, n=92 [63%: 48-83%]; FLH, n=159 [58%: 49-69]; T deficiency, n=326 [47%: 41-54%]; Figure 2; $p < 0.0001$), although this difference was not significant using multivariate analysis.

Pre-transplant presence of malnutrition, pulmonary infection, gut infection, respiratory or liver impairment had a significant deleterious effect on survival (Table 2). Multivariate analysis showed that donor type, pre-existing respiratory impairment, or malnutrition and co-trimoxazole prophylaxis during transplant were strongly significantly associated with outcome (Table 2).

Discussion

This is largest cohort study on the outcome of patients undergoing HSCT for PID, with the longest follow-up. Whilst the data analysis is complex, the large number of patients in the database gives sufficient statistical power to assess outcome trends over different periods. Survival continues to improve over time. Transplantation using a geno-identical sibling donor now gives survival of 90% [95% CI : 77-100%] for SCID patients and 79% [95% CI 69-89%] for patients with non-SCID PID – emphasizing how much safer and successful HSCT has become over time. For selected patients with no pre-existing infection, such as newborns with SCID, the outcome is even better [13, 14]. This data clearly demonstrates an improved outcome when transplanted before 6 months of age. Newborn screening programmes are likely to facilitate the early diagnosis of SCID [15], and thus survival can be expected to improve in the future. Outcome for patients with non-SCID PID is almost as good and continues to improve. As data on long-term outcome of specific PID from national and international registries become available [4, 5, 16], these data regarding outcome of HSCT for particular diseases will help inform clinical decisions for optimal management of these patients. Simple measures including protected environment and co-trimoxazole prophylaxis during transplantation remain important predictors of outcome. Pre-existing lung and liver damage continue to be associated with a poor outcome, as demonstrated in previous studies [7, 17].

The proportion of HLA-mismatched donor transplants for SCID has diminished over time, likely in part to the increasing use of URD transplants. Umbilical cord stem cells, particularly suitable for infant recipients, are being used for an increasing number of patients [8], with 14 cord blood transplants for SCID reported to SCETIDE and 67 to EUROCORD between 1995 and 2005 [18], including geno-identical sibling, and unrelated donor cord blood transplants. A comparative study of unrelated cord blood transplantation versus haploidentical related stem cell transplantation for patients with severe T-cell deficiencies is in preparation with the Eurocord database. A greater use of molecular tissue typing, and hence more accurate identification of HLA matching, is likely to have influenced improved survival for patients receiving stem cells from URD. The increased use of non-conditioned transplants in SCID patients receiving geno-identical stem cells may lead to a more rapid increase in T lymphocyte counts than after URD transplantation, and hence faster clearance of infection. Our data, in contrast to previous reports [19] demonstrates that for patients with SCID, an URD

appears to have no significant advantage over a pheno-identical or HLA mismatched donor, and may take significantly longer to assess before stem cell donation.

On multivariate analysis, for non-SCID patients, survival is better using an unrelated, rather than pheno-identical, donor. The reasons for this are unclear, but could be center effect. Related pheno-identical donors are a mixed group of geno-identical and partially identical donors, but as both pheno-identical related and unrelated donor recipients receive ATG, Campath or OKT3 as part of conditioning, these differences are difficult to explain. The accuracy of HLA typing has improved such that URD are likely to now be a better molecular HLA match than in historic series, thus explaining improvements over time. Survival is almost equivalent to when a geno-identical donor is used, in contra-distinction to SCID patients, where the outcome using a geno-identical donor is better. In the non-SCID group, an URD or other identical relatives show a clear advantage over a haplo-identical donor.

Specific issues arise for different patient groups. In the SCID group, after multivariate analysis, B+ SCID patients have better survival than those with B- SCID, despite improvements in survival in each group over time (data not shown). The effect may be skewed by a large number of artemis-deficient patients in the B- SCID group, a defect associated with poorer outcome, possibly because of the associated generalized cellular radiosensitivity, not confined to cells of hematopoietic origin. However, RAG-deficient B- SCID also has a poorer outcome than B+ SCID [20]. Further explanations include a more hostile micro-thymic environment in some SCID phenotypes, because of a later block in thymocyte development, leading to pre-cursor competition in the thymic niche [21], predisposition to development of autoreactive T cells following engraftment, or organs that are more susceptible to damage by chemotherapy, leading to more veno-occlusive disease or GvHD, for instance in adenosine deaminase-deficient SCID. Additionally, data have not been analyzed with respect to presence or absence of NK cells, in part because of incomplete ascertainment. Some of the results may therefore be attributable not to presence of B lymphocytes, but rather lack of NK cells, which may favour engraftment over rejection [22]. The lack of improvement in survival over the last time period is striking. Patients with SCID are perhaps more difficult to transplant because they are younger at time of transplant, and often have severe opportunistic infection at diagnosis. Additionally, physiologically immature organs including

lungs and liver may be more susceptible to the effects of veno-occlusive disease or GvHD. The presence of more factors of worse prognosis (e.g. more T-B- than T-B+ phenotypes, more mismatched than geno-identical donors) in patients of the third period was sought to help explain an absence of survival improvement between period 2 and period 3 despite improved diagnostic and therapeutic progress. No difference was found that might substantiate this hypothesis, although the analysis may lack power to show a difference (data not shown).

Survival is similar following transplantation for SCID, whether chemotherapy conditioning is used or not. The role of chemotherapy conditioning in the treatment of SCID is unclear [23-26]. There is not adequate detailed data in SCETIDE to comment about the quality of immuno-reconstitution, including production of immunoglobulin and antibody responses to specific protein and polysaccharide antigens, associated with the use or absence of chemotherapy. Increasing evidence from other sources suggests that full immunoreconstitution with long-term T and B lymphogenesis requires stem cell engraftment evidenced by donor myeloid chimerism, at least for some SCID phenotypes [9, 20, 27-29]. The data from SCETIDE need to be interpreted with caution however, as non-conditioned patients are likely to be the most sick, with end-organ damage, who historically would not have tolerated conventional conditioning regimens. Reduced intensity regimens may enable long-term engraftment and immunoreconstution, even in patients with significant end-organ damage [10]. Whilst reduced intensity chemotherapy conditioning is advantageous for patients with significant pre-existing organ damage, the place of fully myeloablative conditioning over reduced intensity chemotherapy is undetermined, and further studies on long-term survival, quality of immunoreconstitution, long-term effects of GvHD, neuro-developmental outcomes and fertility need to be addressed.

An increasing range of non-SCID PID conditions are now treated by HSCT. Changes in proportion of disease categories transplanted over time likely reflect improved diagnosis and better care in early childhood leading to survival in later childhood, so facilitating transplantation at an older age. Survival is not yet as good as for SCID patients, perhaps reflecting the perception that patients need to ‘earn’ the right to transplantation by presenting with significant complications or infections. It is noteworthy that in disease-specific series, outcome is better for younger patients without pre-existing organ damage or infection [17, 30-32]. Overall survival for each disease category is improving over time, but remains poor for undefined T lymphocyte

immunodeficiencies. This may be because without a clear genetic diagnosis, patients are not offered HSCT, in contrast to those with a clearly defined clinical and genetic PID. Interestingly, survival was better for patients transplanted at 12-47 months, rather than <12 or >48 months of age (data not shown). A possible explanation is the inclusion of Omenn syndrome, as well as purine nucleoside phosphorylase and MHC class II deficiencies, in the T lymphocyte immunodeficiency category. These patients are generally transplanted before 12 months of age. Their outcome is poor, possibly explaining the unexpectedly worse outcome in this younger age group in contra-distinction to SCID patients transplanted at the same age (Supplementary Figure E2). A separate analysis of the T lymphocyte deficiency category showed worse outcome for these three diagnoses, and the generally poor overall outcome for the T immunodeficiency group was not skewed by particularly poor results for a specific disease category within the group (Supplementary Figure E6) – as previously demonstrated in disease specific series [33, 34]. Beyond a year survival improves, as well patients with no or minimal organ damage, are treated. Decrease in survival beyond 48 months may reflect treatment of older sicker patients with diseases such as Wiskott-Aldrich syndrome and CD40 ligand deficiency who had more infection and end-organ damage. This study did not look at donor chimerism. Detailed data regarding mixed and mixed split-cell lineage chimerism is not available from the current database, but is important as quanitity of donor chimerism, and the cell lineages in which it is found may impact on quality of immune function [35].

Since the first HSCT for PID in 1968, survival has continued to improve and the range of disorders for which HSCT is considered is expanding. These data from SCETIDE show continuing improvement in survival in all categories. As survival improves, the long-term quality of immuno-reconstitution and other life quality issues become important. Few studies have examined long-term immuno-reconstitution. Significant long-term sequelae are now being identified, including thymic failure in patients without stem cell engraftment [20, 27], appearance of human papilloma virus warts, predominantly in patients with common gamma chain or JAK3-deficient SCID [20, 36], and neurocognitive development in patients post HSCT [37, 38]. It is now critical to analyse the long-term outcome for disease-specific groups. The SCETIDE database is now large enough to begin analysis of outcome of HSCT for different specific genetic defects, for instance RAG- or Artemis deficient T-B-NK+ SCID, although additional data to that routinely collected may be required. The next stage will be to carefully analyse individual disease categories, so that the prognosis following HSCT for the different

genetic conditions may be better understood [39]. Continued careful data collection is required to gain a complete understanding of the outcome for these rare genetic disorders, in order that best treatment can be planned, including the different stem cell therapies and gene therapy [40].

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Authorship

Gennery AR, Slatter MA, helped with data collection, analysis and wrote the manuscript, Landais P, analysed the data and helped write the manuscript, Fischer A, Cavazzana-Calvo M helped with data collection, analysis and helped write the manuscript, Grandin L, Taupin P, helped with data analysis, Cant AJ helped with data analysis and helped write the manuscript, Veys P, Amrolia PJ, Gaspar HB, Davies EG, Friedrich W, Hoenig M, Notarangelo LD, Mazzolari E, Porta F, Bredius RGM, Lankester AC, Wulffraat NM, Seger R, Güngör T, Fasth A, Sedlacek P, Neven B, Blanche S, helped with data collection and helped write the manuscript.

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Figure 1. Cumulative probability of survival in SCID patients after hematopoietic stem cell transplantation according to period in which transplanted, donor source (related or unrelated donor) and HLA matching

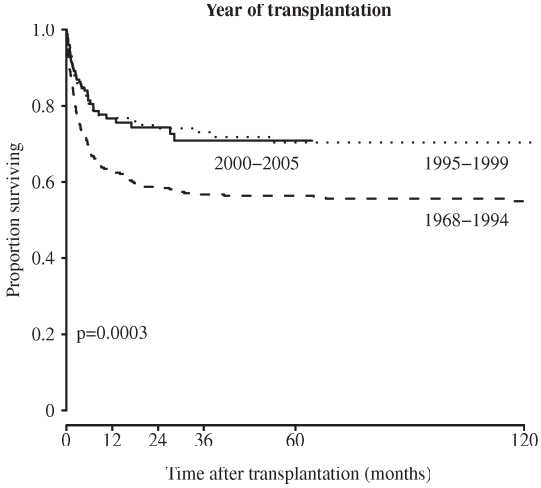
Figure 2. Cumulative probability of survival in T-B- or T- B+ SCID patients after hematopoietic stem cell transplantation through all time periods.

Figure 3. Cumulative probability of survival in non-SCID PID patients after hematopoietic stem cell transplantation according to period in which transplanted, donor source (related or unrelated donor) and HLA matching and type of immunodeficiency through all time periods.

Table 1. Type of immunodeficiency, according to donor origin, HLA matching and year of graft

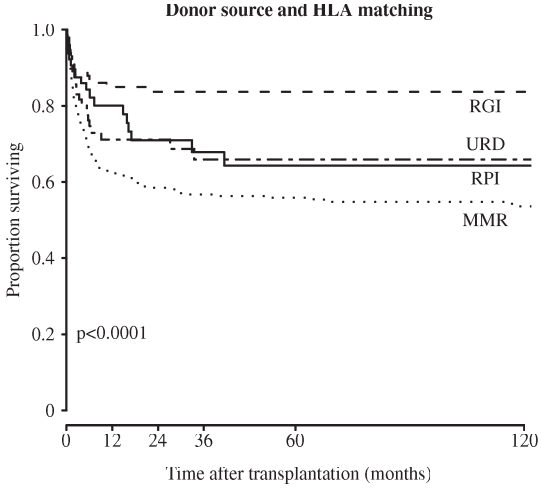
Table 2. Factors affecting outcome after stem-cell transplantation

Year of transplantation

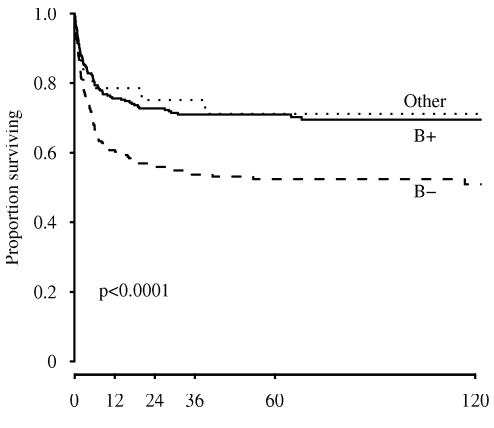


Months	0	6	12	24	36	60	120
Number at risk							
1968–1994	361	245	187	172	166	151	88
1995–1999	157	113	95	78	66	40	3
2000–2005	181	111	74	49	26	4	0

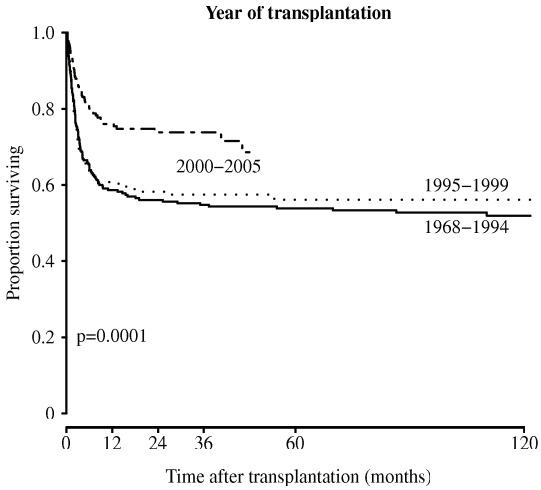
Donor source and HLA matching



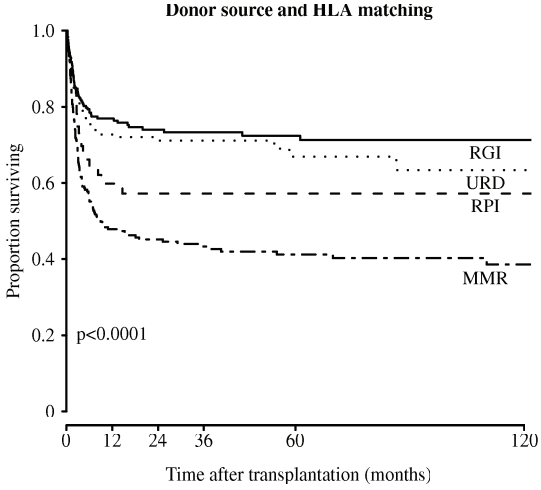
Months	0	6	12	24	36	60	120
Number at risk							
RGI	135	111	77	64	60	50	31
RPI	68	46	36	27	21	16	8
URD	81	53	36	33	23	18	6
MMR	415	259	207	175	154	111	46



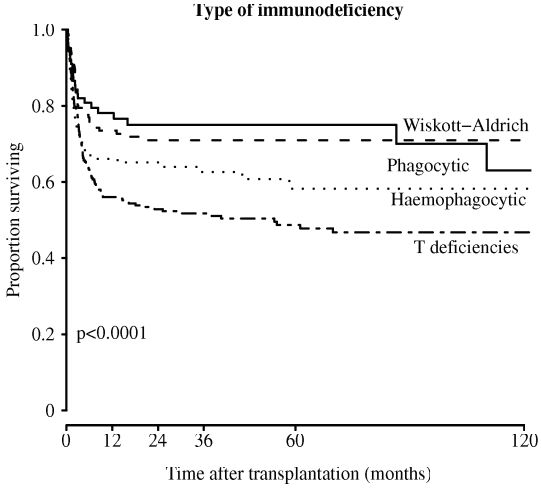
Months	0	6	12	24	36	60	120
Number at risk							
B+	345	247	195	168	147	111	55
B−	300	184	135	109	91	69	33
Other	54	38	26	22	20	15	3



Months	0	6	12	24	36	60	120
Number at risk							
1968–1994	278	179	135	129	125	114	52
1995–1999	238	137	109	79	61	36	5
2000–2005	267	185	123	79	44	0	0



Months	0	6	12	24	36	60	120
Number at risk							
RGI	251	186	138	110	90	67	29
RPI	65	36	25	18	13	9	2
URD	224	151	110	81	60	31	9
MMR	243	128	94	78	67	51	17



Months	0	6	12	24	36	60	120
Number at risk							
T deficiencies	326	181	140	103	82	54	19
Phagocytic disorders	92	71	54	39	30	25	8
Haemophago–cytic syndromes	159	98	69	57	45	22	7
Wiskott–Aldrich syndrome	168	124	91	79	70	55	23

Table 1: Type of immunodeficiency, according to donor origin, HLA matching and year of graft (N: number of patients, %: percentage)

SCID	N	%	Related donor			Unrelated donor
			Genotypically HLA identical	Phenotypically HLA identical	HLA mismatched	
years of graft < 1995						
Total	361		84	33	229	15
Reticular dysgenesis	11	3%	2	1	7	1
ADA deficiency	42	12%	14	1	25	2
T- B-	105	29%	29	14	60	2
T- B+	181	50%	34	13	127	7
Other	22	6%	5	4	10	3
years of graft [1995-1999]						
Total	157		26	21	90	20
Reticular dysgenesis	3	2%	0	0	3	0
ADA deficiency	15	10%	6	4	2	3
T- B-	46	29%	3	11	25	7
T- B+	80	51%	11	4	57	8
Other	13	8%	6	2	3	2
years of graft [2000-02005]						
Total	181		25	14	96	46
Reticular dysgenesis	5	3%	0	0	4	1
ADA deficiency	18	10%	5	1	4	8
T- B-	55	30%	7	5	32	11
T- B+	84	46%	9	7	52	16
Other	19	11%	4	1	4	10
Non-SCID						
years of graft < 1995						
Total	278		103	17	130	28
Wiskott-Aldrich syndrome	85	30%	30	3	40	12
T-cell deficiencies						
Omenn syndrome	21	8%	4	2	12	3
PNP deficiency	3	1%	1	1	1	0
HLA class II deficiency	36	13%	13	3	18	2
CD40 ligand deficiency	1	0%	1	0	0	0
Other	41	15%	13	1	25	2
Phagocytic-cell disorders						
Agranulocytosis	5	2%	3	0	2	0
Chronic granulomatous disorders	11	4%	7	0	0	4
Leucocyte adhesion deficiency	19	7%	6	1	11	1
Haemophagocytic syndromes						
Familial lymphohistiocytosis	33	12%	14	1	16	2
Chediak-Higashi syndrome	15	5%	7	4	2	2
XLP (Purtillo)	0	0%	0	0	0	0
Gricelli's disease	2	1%	2	0	0	0
Other	6	2%	2	1	3	0

Table 1: Type of immunodeficiency, according to donor origin, HLA matching and year of graft (N: number of patients, %: percentage) (continued)

Non-SCID	N	%	Related donor			Unrelated donor
			Genotypically HLA identical	Phenotypically HLA identical	HLA mismatched	
years of graft [1995-1999]						
Total	238		75	25	66	72
Wiskott-Aldrich syndrome	34	14%	10	4	8	12
T-cell deficiencies						
Omenn syndrome	24	10%	6	1	12	5
PNP deficiency	1	0%	1	0	0	0
HLA class II deficiency	17	7%	4	7	5	1
CD40 ligand deficiency	18	8%	4	0	0	14
Other	65	27%	20	6	18	21
Phagocytic-cell disorders						
Agranulocytosis	0	0%	0	0	0	0
Chronic granulomatous disorders	9	4%	9	0	0	0
Leucocyte adhesion deficiency	8	3%	3	1	4	0
Other	6	3%	3	1	1	1
Haemophagocytic syndromes						
Familial lymphohistiocytosis	33	14%	6	3	15	9
Chediak-Higashi syndrome	5	2%	3	0	0	2
XLP (Purtillo)	4	2%	2	0	0	2
Gricelli's disease	6	3%	2	1	2	1
Other	8	3%	2	1	1	4
years of graft [2000-2005]						
Total	267		73	23	47	124
Wiskott-Aldrich syndrome	49	18%	8	3	3	35
T-cell deficiencies						
Omenn syndrome	20	8%	3	4	9	4
PNP deficiency	7	3%	0	2	2	3
HLA class II deficiency	9	3%	2	0	5	2
CD40 ligand deficiency	17	6%	5	0	1	11
Other	46	17%	15	2	7	22
Phagocytic-cell disorders						
Agranulocytosis	5	2%	0	0	0	5
Chronic granulomatous disorders	21	8%	13	0	0	8
Leucocyte adhesion deficiency	7	3%	4	0	3	0
Other	1	0%	1	0	0	0
Haemophagocytic syndromes						
Familial lymphohistiocytosis	33	12%	8	4	9	12
Chediak-Higashi syndrome	6	2%	1	2	1	2
XLP (Purtillo)	15	6%	1	0	5	9
Gricelli's disease	7	3%	3	2	0	2
Other	24	9%	9	4	2	9

Table 2: Factors affecting outcome after stem-cell transplantation

SCID	Univariate analysis				Multivariate analysis	
	Patients	Deaths	10-Survival % (95% CI)	p	Hazard ratio (95% CI)	p
Years of graft						
2000-2005	181	41	71 (63-80)[1]	0.0003	1	
1995-1999	157	40	70 (63-79)[1]		1.0 (0.6-1.7)	0.97
<1995	361	153	56 (51-62)[1]		1.5 (1.0-2.2)	0.06
Age at transplantation						
<6 months	289	79	68 (62-74)	0.0008	1	
6-11 months	253	92	59 (53-67)		1.3 (0.9-1.9)	0.11
>12 months	145	61	51 (42-61)		2.4 (1.6-3.5)	<0.0001
SCID phenotype						
B+	345	92	70 (64-76)	<0.0001	1	
B-	300	128	51 (45-58)		2.2 (1.6-2.9)	<0.0001
Other	54	14	71 (58-87)		1.2 (0.7-2.2)	0.55
Recipient/donor compatibility						
Related genotypically identical	135	20	84 (77-91)	<0.0001	1	
Related phenotypically identical	68	18	64 (52-80)		2.6 (1.3-5.3)	0.009
Unrelated donor	81	23	66 (55-79)		4.1 (2.1-8.1)	0.0001
Related HLA mismatched	415	173	54 (48-60)		8.9 (4.6-17.2)	<0.0001
Respiratory Impairment						
No	379	123	63 (58-69)	0.006	1	
Yes	247	102	55 (48-62)		1.6 (1.2-2.2)	0.002
Septicaemia						
No	563	197	61 (56-65)	0.003	1	
Yes	53	27	46 (33-63)		1.8 (1.1-2.8)	0.013
Viral infection						
No	432	144	63 (58-68)	0.002	1	
Yes	191	81	52 (45-61)		1.4 (1.0-1.9)	0.041
T-cell depletion						
Yes	422	160	57 (52-63)	0.011	1	
No	266	71	69 (63-76)		2.0 (1.3-3.3)	0.004
Protected environment						
Yes	613	199	63 (59-67)	0.004	1	
No	55	26	50 (37-66)		2.0 (1.2-3.2)	0.005
Prophylaxis[2]						
Yes	503	173	62 (57-67)	0.021	1	
No	88	40	54 (44-66)		1.9 (1.3-2.8)	0.0007

Table 2: Factors affecting outcome after stem-cell transplantation (continued)

Non SCID	Univariate analysis				Multivariate analysis	
	Patients	Deaths	10-Survival % (95% CI)	p	Hazard ratio (95% CI)	p
Years of graft						
2000-2005	267	65	69 (60-78)[3]	0.0001	1	
1995-1999	238	93	58 (51-65)[3]		1.7 (1.2-2.5)	0.005
<1995	278	126	54 (49-61)[3]		1.4 (1.0-2.0)	0.09
Recipient/donor compatibility						
Related genotypically identical	251	63	71 (65-78)	<0.0001	1	
Related phenotypically identical	65	24	57 (45-72)		1.9 (1.1-3.2)	0.021
Unrelated donor	224	63	63 (54-74)		1.2 (0.8-1.9)	0.29
Related HLA mismatched	243	134	39 (32-47)		2.4 (1.7-3.3)	<0.0001
Respiratory Impairment						
No	522	176	61 (56-67)	<0.0001	1	
Yes	150	76	43 (34-53)		1.5 (1.1-2.1)	0.012
Malnutrition						
No	562	187	62 (57-67)	0.0004	1	
Yes	145	74	44 (35-54)		1.5 (1.1-2.0)	0.017
Prophylaxis[2]						
Yes	590	204	60 (56-65)	<0.0001	1	
No	91	55	33 (23-48)		2.4 (1.7-3.3)	<0.0001

[1]: 5-Survival is given; [2]: trimethoprim-sulfamethoxazole; [3]: 4-Survival.

Online Repository

Transplantation of Hematopoietic Stem Cells and Long Term Survival for Primary Immunodeficiencies in Europe: entering a new century, do we do better?

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Effect of conditioning on outcome.

Conditioning was performed in accordance with guidelines current at time of transplantation. A complementary analysis is presented considering the "conditioning" variable composed of 4 classes: no conditioning, busulfan containing, other chemotherapy without busulfan, and ATG, Campath or OKT3 only (supplementary Table E3). Whilst 42% of SCID patients did not receive conditioning, only 5% of non SCID PID patients were not conditioned. The outcome using busulfan was no better than not giving conditioning, although close to statistical significance (HR: 1.4; 95% CI [1.0-2.1] P=0.05). This result was expected since recipients receiving stem cells from geno-identical donors as well as those with T-B+ PID did not often receive conditioning.

The outcome using busulfan appeared better than using non-busulfan regimens (HR: 2.1; 95% CI [1.3-3.3] P=0.002) (supplementary Table E3). The outcome using busulfan did not appear better than using ATG, Campath or OKT3 alone (HR: 1.1; 95% CI [0.5-2.3] p =NS), although the number of patients who received ATG, Campath or OKT3 alone was limited (n=29).

In Non-SCID PID patients survival following transplantation using busulfan conditioning was not statistically different to using no conditioning, other chemotherapy, or ATG, Campath or OKT3 alone.

Supplementary Figure E1. Cumulative probability of survival in SCID patients after hematopoietic stem cell transplantation according to year at grafting in HLA mismatched SCID

Supplementary Figure E2. Cumulative probability of survival in SCID patients after hematopoietic stem cell transplantation according to age at transplantation through all time periods

Supplementary Figure E3. Cumulative probability of survival in SCID patients after hematopoietic stem cell transplantation according to donor source (related or unrelated donor) and HLA matching for the period 2000-2005

Supplementary Figure E4. Cumulative probability of survival in non-SCID PID patients after hematopoietic stem cell transplantation according to donor source (related or unrelated donor) and HLA matching for the period 2000-2005

Supplementary Figure E5. Cumulative probability of survival in non-SCID PID patients after hematopoietic stem cell transplantation according to type of T cell deficiency for the period 1995-2005.

Supplementary Table E1: Clinical characteristics of patients according to year of graft

SCID	Related donor			Unrelated donor
	Genotypically HLA identical	Phenotypically HLA identical	HLA mismatched	
years of graft < 1995				
Total	84	**33**	229	15
More than one stem-cell transplantation	8	3	43	4
Median age at transplantation (months)	5.8	6.2	7.2	13.1
<6	46	15	87	2
6-11	20	17	98	2
12-18	8	0	27	6
>18	8	1	15	5
Year of transplantation				
1968-85	34	14	57	4
1986-90	27	11	89	0
1991-94	23	8	83	11
Conditioning	**20**	**12**	**160***	**11**
Median (range) follow-up (years)	8.8 (0.5-27.8)	9.6 (0.5-32.6)	9.3 (0.5-22.3)	8.9 (5.3-12.8)
3-year Survival % (95% CI)	**81 (73-90)**	**57 (41-78)**	**49 (43-56)**	**53 (33-86)**
years of graft [1995-1999]				
Total	26	21	90	20
More than one stem-cell transplantation	3	2	17	2
Median age at transplantation (months)	6.6	4.5	6.9	10.1
<6	12	11	34	6
6-11	6	4	40	8
12-18	5	2	6	2
>18	2	3	8	3
Conditioning	**7**	**2**	**63**	**15**
Median (range) follow-up (years)	2.0 (0.4-9.6)	2.5 (0.4-6.2)	4.5 (0.2-10.8)	7.1 (0.9-10.4)
3-year Survival % (95% CI)	**84 (69-100)**	**80 (62-100)**	**69 (60-79)**	**68 (48-97)**
years of graft [2000-2005]				
Total	25	14	96	46
More than one stem-cell transplantation	0	2	23	5
Median age at transplantation (months)	4.9	4.2	7.5	9.5
<6	16	9	33	18
6-11	5	2	41	10
12-18	2	0	6	7
>18	2	3	13	11
Conditioning	**3**	**4**	**78***	**37**
Median (range) follow-up (years)	1.0 (0.5-2.1)	1.2 (0.4-4.9)	1.4 (0.2-5.0)	1.8 (0.2-5.4)
3-year Survival % (95% CI)	**90 (77-100)**	**83 (58-100)**	**66 (55-78)**	**69 (54-89)**

* Missing data for one patient of this group.

Supplementary Table E1: Clinical characteristics of patients according to year of graft (continued)

Non-SCID	Related donor			Unrelated donor
	Genotypically HLA identical	Phenotypically HLA identical	HLA mismatched	
years of graft < 1995				
Total	103	17	130	28
More than one stem-cell transplantation	8	2	21	1
Median age at transplantation **(months)**	30.6	21.9	17.7	34.4
<12 months	29	6	42	5
12-23 months	16	3	38	8
2-3 years	19	4	27	8
>4 years	39	4	22	7
Year of transplantation				
1968-85	31	6	21	4
1986-90	32	6	57	3
1991-94	40	5	52	21
Conditioning	**96***	**16**	**128**	**28**
Median (range) follow-up (years)	8.6 (0.5-18.6)	9.5 (0.5-14.6)	8.7 (0.1-16.6)	9.1 (0.5-13.9)
3-year Survival % (95% CI)	**72 (63-81)**	**46 (27-78)**	**41 (33-51)**	**66 (50-87)**
years of graft [1995-1999]				
Total	75	25	66	72
More than one stem-cell transplantation	1	6	15	4
Median age at transplantation **(months)**	50.5	19.2	18.2	50.1
<12 months	19	4	22	10
12-23 months	4	10	18	14
2-3 years	13	3	10	11
>4 years	39	8	13	37
Conditioning	**70***	**25**	**63**	**70**
Median (range) follow-up (years)	2.7 (0.2-10.9)	1.8 (0.2-5.5)	2.6 (0.2-10.4)	3.8 (0.1-11.2)
3-year Survival % (95% CI)	**71 (60-83)**	**53 (36-78)**	**41 (30-57)**	**60 (49-73)**
years of graft [2000-2005]				
Total	73	23	47	124
More than one stem-cell transplantation	6	4	14	17
Median age at transplantation **(months)**	38.5	24.2	19.7	36.5
<12 months	19	8	19	23
12-23 months	6	3	9	25
2-3 years	16	8	9	23
>4 years	31	4	10	52
Conditioning	**67***	**21**	**43**	**113**
Median (range) follow-up (years)	1.5 (0.0-5.0)	1.2 (0.3-3.9)	2.3 (0.4-5.0)	1.4 (0.2-5.0)
3-year Survival % (95% CI)	**79 (69-89)**	**76 (57-100)**	**55 (42-72)**	**79 (71-87)**

* Missing data for one patient of this group.

Supplementary Table E2. Type of conditioning according to year of transplantation and diagnosis: SCID (1968-2005, N=699).

	No Conditioning (n= 285)	Busulphan contain. (n=297)	Other chemotherapy (n= 69)	ATG, Campath or OKT3 only (n=29)	Other Conditioning or n.a. (n=19)	Stat
<1995	55.09 %	44.11 %	50.72 %	68.97 %	100%	Fisher
1995-1999	24.56 %	24.58 %	15.94 %	10.34 %	0%	0.00001
2000-2005	20.35 %	31.31 %	33.33 %	20.69 %	0%	
Reticular Dysgenesis	0.7 %	3.37 %	2.9 %	3.37 %	13.79 %	Fisher
ADA deficiency	14.74 %	5.39 %	7.25 %	5.39 %	13.79 %	0.00001
T-B-	30.88 %	29.63 %	30.43 %	29.63 %	10.34 %	
T-B+	49.82 %	53.87 %	39.13 %	53.87 %	48.28 %	
Other	3.86 %	7.74 %	20.29 %	7.74 %	13.79 %	
Geno ident.	36.84 %	5.05 %	11.59 %	13.79 %	17.65 %	Fisher
Pheno ident.	17.54 %	2.69 %	7.25 %	6.9 %	17.65 %	0.00001
URD	6.32 %	14.14 %	24.64 %	13.79 %	0%	
Mismatch	39.3 %	78.11 %	56.52 %	65.52 %	64.71 %	

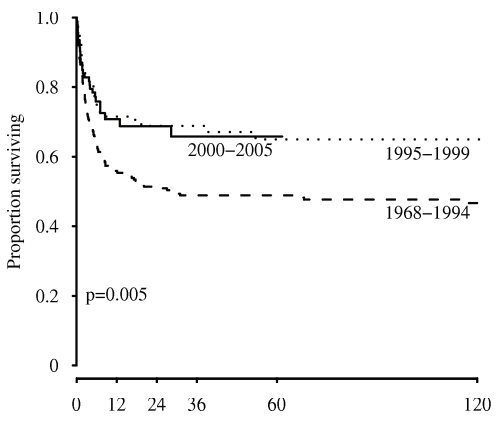
Supplementary Table E2 (Continued). Type of conditioning according to year of transplantation and diagnosis: Non SCID (1968-2005, N=783).

	Conditioning no (n= 40)	Busulphan contain. (n= 499)	Other chemotherapy (n= 116)	ATG, Campath or OKT3 only (n=55)	Other Conditioning or n.a. (73)	Stat
<1995	22.5 %	23.85 %	29.31 %	81.82 %	100%	χ^2
1995-1999	22.5 %	37.47 %	31.03 %	9.09 %	0%	<0.00001
2000-2005	55%	38.68 %	39.66 %	9.09 %	0%	
Geno	37.5 %	31.46 %	25%	10.91 %	58.57 %	Fisher
Pheno	7.5 %	9.22 %	4.31 %	7.27 %	10%	<0.00001
Mud	32.5 %	31.66 %	42.24 %	7.27 %	0%	
Mismatch	22.5 %	27.66 %	28.45 %	74.55 %	31.43 %	

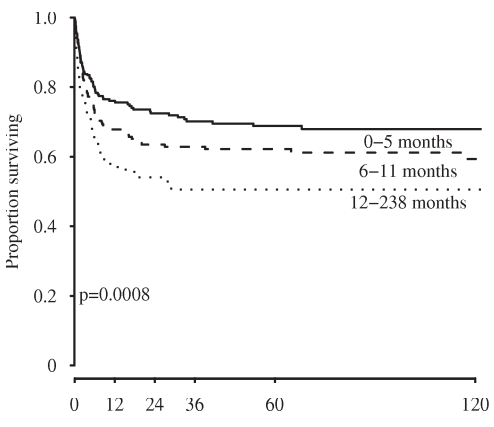
Supplementary Table E3. Outcome of transplantation according to type of conditioning regimen used for SCID and non-SCID PID patients.

Variables: SCID	**HR***	**95% CI***	**p***
Conditioning : no conditioning vs busulfan	1.4	1.0-2.1	0.05
other chemotherapy vs busulfan	2.1	1.3-3.3	0.002
ATG, Campath or OKT3 only vs busulfan	1.1	0.5-2.3	0.84
Variables: Non-SCID PID			
Conditioning : no conditioning vs busulfan	1.4	0.7-2.7	0.29
other chemotherapy vs busulfan	1.4	0.9-2.0	0.12
ATG, Campath or OKT3 only vs busulfan	1.3	0.8-2.0	0.33

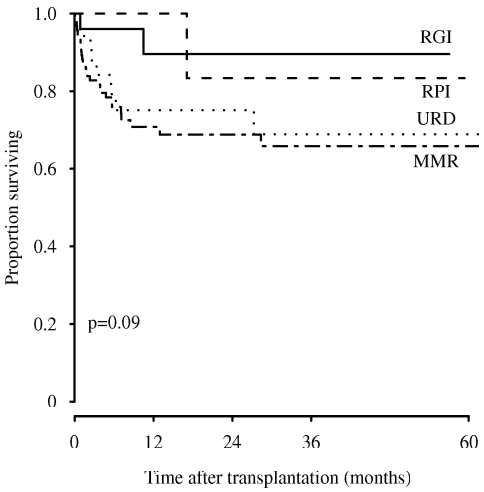
*Cox proportional hazard model: HR hazard ratio 95% confidence interval



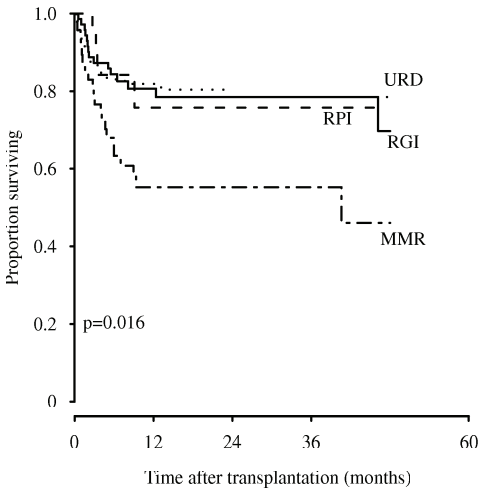
Months	0	6	12	24	36	60	120
Number at risk							
1968–1994	229	144	113	101	96	86	45
1995–1999	90	65	57	49	43	23	1
2000–2005	96	50	37	25	15	2	0



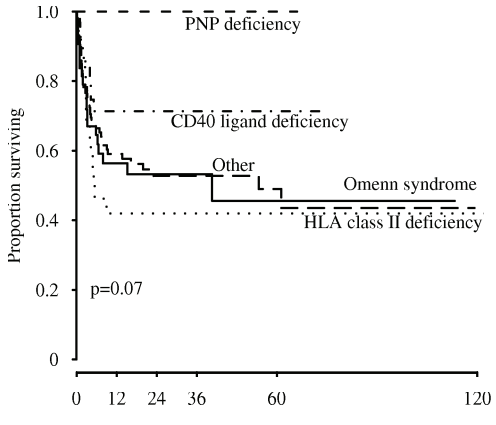
Months	0	6	12	24	36	60	120
Number at risk							
0–5 months	289	210	158	135	118	92	47
6–11 months	253	170	134	110	94	70	32
12–238 months	145	80	56	48	40	28	12



Months	0	6	12	24	36	60
Number at risk						
RGI	25	22	12	6	3	0
RPI	14	9	7	2	1	0
URD	46	30	18	16	7	2
MMR	96	50	37	25	15	2



Months	0	6	12	24	36	60
Number at risk						
RGI	73	55	37	20	13	0
RPI	23	14	8	5	2	0
URD	124	88	60	41	21	0
MMR	47	28	18	13	8	0



Months	0	6	12	24	36	60	120
Number at risk							
Omenn syndrome	44	26	19	11	9	3	0
PNP deficiency	8	5	4	2	1	1	0
HLA class II deficiency	26	11	10	8	4	1	1
CD40 ligand deficiency donor	35	21	17	11	4	3	0
Other	111	60	45	28	24	10	0