

## Special report

# Outcome of 5651 hematopoietic stem cell transplants for hematological malignancies carried out in Europe in 1993: a reliability study of the registry

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### Summary:

Outcome results of observational databases are frequently criticized as relying on incomplete information from incomplete patient populations. Few data are available to dispute these arguments of selection bias. The European Group for Blood and Marrow transplantation (EBMT) decided to address this question by evaluating the hematopoietic stem cell transplants performed in 1993. A comprehensive survey was launched in an effort to collect informations on all transplants for hematological malignancies performed throughout Europe during the year 1993. The main goals of this effort were to compare the group of spontaneously reported patients with the group of retrospectively solicited patients, and to give an accurate estimate of the outcome of all patients. For the year 1993, the annual EBMT activity survey indicated 6336 transplants performed for hematological malignancies in Europe. A total of 5651 transplants could be analyzed; 2595 were reported spontaneously by the teams (group A) and 3056 were retrieved on solicitation (group B). Patients and transplant characteristics for group A and B were very similar for most parameters with a few exceptions. There was no statistical difference for outcome at 3 years between groups A and B: disease-free survival (DFS) was  $45 \pm 1\%$  and  $44 \pm 1\%$ , relapse incidence (RI)  $41 \pm 1\%$  and  $42 \pm 1\%$ , transplant-related mortality (TRM)  $23 \pm 1\%$  and  $23 \pm 1\%$ , and overall survival (OS)  $54 \pm 1\%$  and  $55 \pm 1\%$ , respectively, for group A and group B. The real outcome at 3 years for the 5651 patients (group A + group B) transplanted in 1993 was  $44 \pm 1\%$ ,  $41 \pm 1\%$ ,  $23 \pm 1\%$ , and  $54 \pm 1\%$ , for DFS, RI, TRM and OS, respectively. The outcome at 3 years by transplant modality, autologous or allogeneic

transplants, and by disease categories showed no difference between groups A and B.

*Bone Marrow Transplantation* (2002) 30, 637–643.  
doi:10.1038/sj.bmt.1703712

**Keywords:** hematopoietic stem cell transplantation; observational vs solicited data; actual outcome

A considerable number of scientific observations and analyses have been obtained from data collected retrospectively at centralized registries, which have contributed to the progress of medicine in various ways. In the field of hematopoietic stem cell transplantation, information for the past 20 years has been obtained essentially from two registries, the International Bone Marrow Transplantation Registry (IBMTR)<sup>1,2</sup> based in Milwaukee (USA), and the disease-oriented registries of the European Group for Blood and Marrow transplantation (EBMT)<sup>1–7</sup> handled by working parties in various locations throughout Europe with centralized management offices in Paris and London. These registries have contributed to the identification of numerous prognostic factors for the treatment of various diseases and to the design of technical improvements for successful transplants. Several prospective randomized studies have been built from and have indeed confirmed many observations first obtained from the registries.

Analyses from registries have been criticized as relying on suboptimal and nonconsecutive data reporting from voluntary teams only, with lack of internal or outside data quality controls. Suspicion has been raised that reported data are biased and have not in fact been an objective reflection of the reality.

The EBMT has two independent data collection procedures. The first, the EBMT activity survey has provided information on the total number of patients transplanted in Europe by each team, year by year, since 1990, according to diagnosis, donor type and stem cell source. The second has consisted of collecting detailed information on patients, diseases, transplant and outcome for retrospective scientific

analyses. This second procedure has not concerned all transplants and has depended on interest, commitment and possibilities of individual teams, on a regular voluntary basis.

In 1995, a comprehensive survey was launched in an effort to collect standardized information on all transplants for all diseases performed throughout Europe during the year 1993. The main goals of this effort were to compare the group of patients reported spontaneously with the group of those solicited retrospectively and to give an accurate estimate of outcome following autologous or allogeneic hematopoietic stem cell transplantation for hematological malignancies by providing a precise picture of what really occurred to these patients transplanted in Europe during the year 1993.

## Patients and methods

### Study design

This is a retrospective study which focused on patients transplanted with autologous or allogeneic hematopoietic stem cells in 1993 for hematological malignancies.

The first endpoint was to assess and to compare two separate cohorts of patients: a group of patients whose data were present in the database and were spontaneously reported by the teams on a voluntary basis (group A, spontaneous group) and a group of patients whose data were retrieved on solicitation by the study committee (group B, solicited group). Information on missing data was obtained from the EBMT activity survey 1993.<sup>4</sup>

The second endpoint was to give the real outcome of patients with hematological malignancies transplanted with autologous or allogeneic hematopoietic stem cells in Europe in 1993.

For the year 1993, the annual EBMT activity survey indicated 6336 hematopoietic transplants performed in Europe for hematological malignancies, consisting of 3557 autologous transplants and 2779 allogeneic transplants.

Of these 6336 transplants, 3172 (50.06%) were reported spontaneously; 3164 transplants (49.94%) were missing. EBMT teams were requested to forward the missing information for all patients not yet reported and at the same time to give an updated follow-up for all patients. Teams were contacted repeatedly by the investigators until delivery of the full data.

### Data collection

Data were collected by standardized questionnaire or electronic database system according to the Minimum Essential Data A form which includes information on patient identification, disease characteristics, transplant details on donor type, stem cell source and minimal information on outcome.

### Definition of endpoints

Both groups were compared for distribution of patients and disease characteristics including patient age, gender, diag-

nosis, stage of disease at transplant, time from diagnosis to transplant (days), source of stem cells and total body irradiation (TBI) in the conditioning regimen.

Outcome analysis concentrated on probabilities of survival (OS), transplant-related mortality (TRM), relapse incidence (RI) and disease-free survival (DFS). DFS was defined as survival without evidence of relapse, the event under study being death or relapse. To evaluate the probability of RI, patients dying either from direct toxicity or from any other cause not related to leukemia were censored. TRM was defined as death while in complete remission. Patients were censored at the time of relapse or at the last follow-up.<sup>8</sup> Probabilities at 3 years were evaluated first for all patients transplanted in 1993 whatever the type of transplant and disease category, then separately for autologous and allogeneic transplantation whatever the disease category, and finally for autologous and allogeneic transplantation by disease category. For each of these evaluations results were given the population A and B. Outcome between population A and B was compared.

Outcomes for allogeneic transplantation were separated between outcome of genotypical allogeneic transplants and outcome of other allogeneic transplants comprising syngeneic, other family related and unrelated allogeneic transplants. When the number of patients in a subgroup was too small (below 30), outcome was not analyzed. To avoid false interpretations, we used the two-tailed *P* values.

### Statistical analysis

All analyses were performed with the SPSS computer program (SPSS Inc, Chicago, IL, USA). Values reported for quantitative variables were median and range. Comparisons of the two groups A and B were with the chi-square and the Mann-Whitney *U*-test. DFS, RI, TRM and OS were estimated by the product-limit method.<sup>9</sup> The significance of differences between curves was estimated by the log-rank test (Mantel-Cox).

## Results

### Population

By June 1998, a total of 5945 patient data forms had been collected from 323 teams in Europe (see appendix) corresponding to 93.8% of the 6336 transplants reported in 1993. From these 5945 transplants, 294 second or subsequent transplants were removed for the analysis. The final analysis was restricted to a population of 5651 patients with first transplants: 2595 patients in group A and 3056 patients in group B.

### Distribution

The total population (A + B) of 5651 patients consisted of 60% males and 40% females, with a median age of 34 years (range: 1–70); 16% were children (age  $\leq$  16 years old). Autologous transplantation was performed for 3171 patients (56%) and allogeneic transplantation for 2480 (44%). Almost half of the patients (44%) were transplanted

in first complete remission (or in first chronic phase for CML). For autologous transplantation, 57% of patients received bone marrow as source of stem cells, 34% peripheral blood and 9% both. For allogeneic transplantation 99.3% of patients received bone marrow and 0.7% peripheral blood.

Distribution of autologous transplants, allogeneic transplants and disease categories in the total population A + B, group A and group B is shown in Table 1.

Comparison of distribution between group A and group B indicated no statistical difference for age, sex ratio, source of stem cell except for a higher proportion of autologous transplants in group A (59%) than in group B (54%) ( $P < 0.0001$ ) and more allogeneic transplantation done in first complete remission in group A (59%) than in group B (45%) ( $P < 0.0001$ ).

*Comparison of distribution by disease between group A and group B*

Comparison showed that for autologous transplantations performed for hematological malignancies, both groups were similar for most disease characteristics with a few exceptions listed below shown in group A compared to group B:

- In non-Hodgkin's lymphomas: a shorter median time from diagnosis to transplant (320 versus 398 days,  $P = 0.001$ ), more TBI (63% vs 29%,  $P < 10^{-4}$ ); marrow more frequently used as the source of stem cells (50% vs 44%,  $P < 10^{-4}$ ).
- In Hodgkin's disease: a lower proportion of children (2% vs 7%,  $P = 0.01$ ) and less TBI (8% vs 56%,  $P < 10^{-4}$ ).
- In multiple myeloma: more patients classified as responding to chemotherapy at the time of transplant

**Table 1** Distribution of patients with hematological malignancies transplanted in 1993, by type of transplant and by disease category in group A, group B and the total population A + B

	Group A	Group B	Total population A + B
All transplants	2595	3056	5651
Autologous transplants	1537	1634	3171
Allogeneic transplants	1058	1422	2480
Genoidentical	831	1009	1840
Syngeneic	11	10	21
Other family related	86	116	202
Unrelated	122	216	338
Missing information	8	71	79
Disease categories			
Acute myeloid leukemia	471	713	1184
Acute lymphoid leukemia	390	497	887
Myelodysplastic syndrome	76	95	171
Secondary acute leukemia	29	22	51
Chronic myeloid leukemia	331	417	748
Chronic lymphoid leukemia	6	13	19
Non-Hodgkin's lymphoma	814	491	1305
Hodgkin's disease	259	312	571
Multiple myeloma	138	337	475
Aplastic anemia	81	159	240

(77% vs 65%,  $P = 0.03$ ) and less TBI (35% vs 76%,  $P < 10^{-4}$ ).

- In acute leukemias: more TBI for acute myeloid leukemia (78% vs 52%,  $P < 10^{-4}$ ) and for acute lymphocytic leukemia (92% vs 54%,  $P < 10^{-4}$ ), and more patients transplanted in first complete remission for acute lymphocytic leukemia (75% vs 51%,  $P < 10^{-4}$ ).

Comparison for allogeneic transplants for hematological malignancies indicated no difference for most parameters with a few exceptions listed below, shown in group A compared to group B:

- In acute myeloblastic leukemia: a longer median time from diagnosis to transplantation (202 vs 160 days,  $P < 10^{-4}$ ) and a higher proportion of allogeneic identical sibling transplantation (91% vs 82%,  $P = 0.002$ ).
- In acute lymphocytic leukemia: a higher median age (20 vs 15 years old,  $P < 10^{-4}$ ) and fewer children (42% vs 55%,  $P = 0.003$ ); a shorter median time from diagnosis to transplantation (242 vs 549 days,  $P = 0.0001$ ); more patients transplanted in first complete remission (64 vs 35%,  $P < 10^{-4}$ ), and a higher proportion of identical sibling allogeneic transplants (76% vs 67%,  $P = 0.02$ ).
- In myelodysplastic syndromes: a higher median age (38 vs 31 years old,  $P = 0.03$ ); less patients receiving TBI (63% vs 88%,  $P = 0.003$ ).
- In chronic myeloid leukemia: more patients transplanted in first chronic phase (76% vs 66%,  $P = 0.005$ ).
- In multiple myeloma: more female donors (56% vs 33%,  $P = 0.04$ ).

*Outcome at 3 years*

On comparison of outcome between groups A and B at 3 years, with all patients combined, whatever the type of transplant and the disease category, there was no statistical difference.

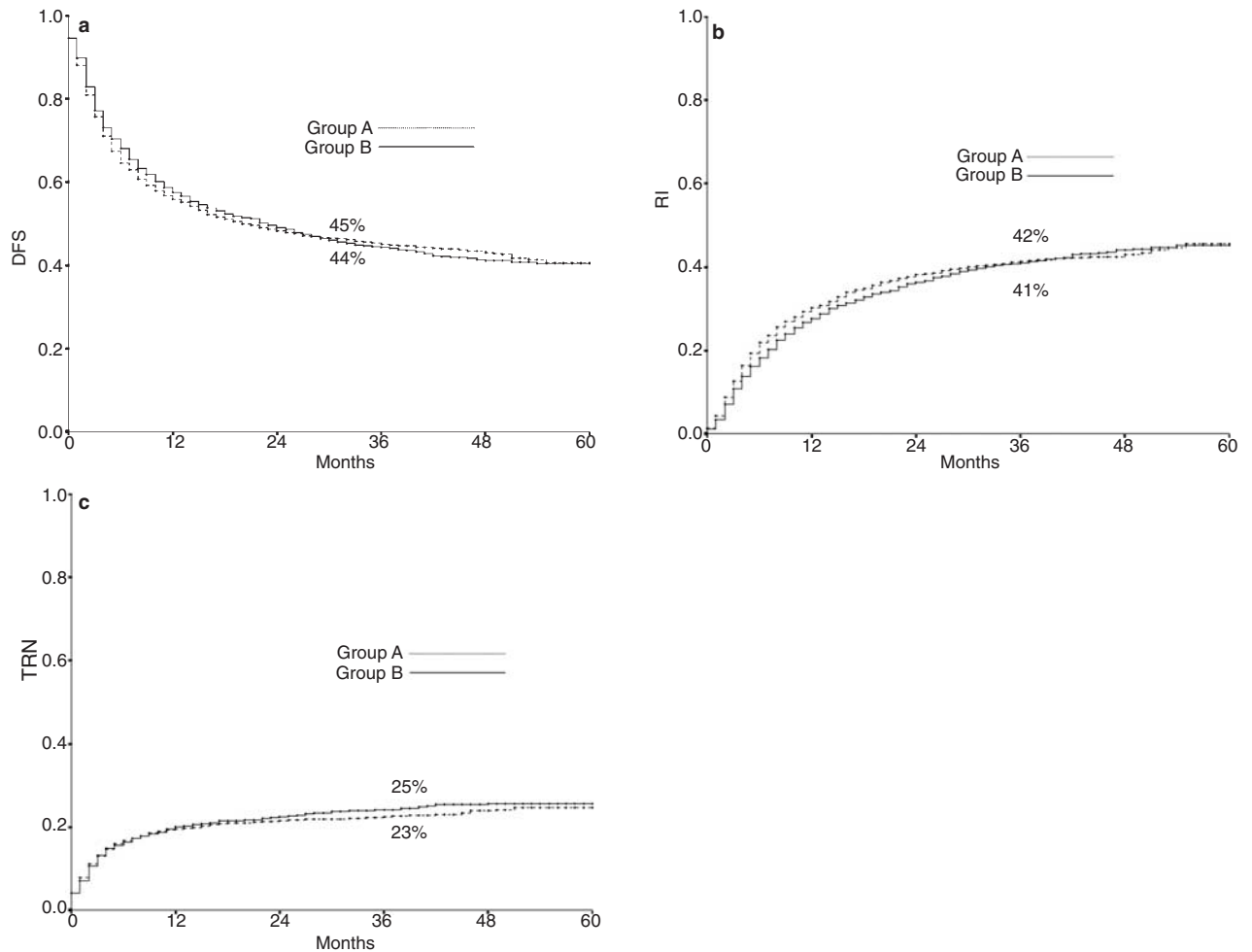
DFS was  $45 \pm 1\%$  and  $44 \pm 1\%$  ( $P = 0.68$ ) (Figure 1a), RI  $41 \pm 1\%$  and  $42 \pm 1\%$  ( $P = 0.76$ ) (Figure 1b), TRM  $23 \pm 1\%$  and  $25 \pm 1\%$  ( $P = 0.29$ ) (Figure 1c) and OS  $54 \pm 1\%$  and  $55 \pm 1\%$  ( $P = 0.52$ ), respectively.

Real outcome for the 5561 patients (group A + group B) transplanted in 1993 was  $45 \pm 1\%$ ,  $41 \pm 1\%$ ,  $23 \pm 1\%$ , and  $54 \pm 1\%$ , for DFS, RI, TRM and OS, respectively.

Results for group A and group B by type of transplant showed no statistical difference between the two groups.

For autologous transplants, DFS was  $44 \pm 1\%$  and  $45 \pm 1\%$  ( $P = 0.33$ ), RI  $49 \pm 1\%$  and  $47 \pm 1\%$  ( $P = 0.16$ ), TRM  $13 \pm 1\%$  and  $15 \pm 1\%$  ( $P = 0.53$ ) and OS  $56 \pm 1\%$  and  $58 \pm 1\%$  ( $P = 0.09$ ) for group A and group B, respectively. The real outcome at 3 years of all autologous transplants (group A + group B) was  $45 \pm 1\%$ ,  $48 \pm 1\%$ ,  $14 \pm 1\%$  and  $57 \pm 1\%$  for DFS, RI, TRM and OS, respectively.

For genoidentical allogeneic transplants DFS was  $50 \pm 2\%$  and  $48 \pm 2\%$  ( $P = 0.51$ ), RI  $27 \pm 2\%$  and  $30 \pm 2\%$  ( $P = 0.24$ ), TRM  $31 \pm 2\%$  and  $31 \pm 2\%$  ( $P = 0.84$ ) and OS  $55 \pm 2\%$  and  $53 \pm 2\%$  ( $P = 0.55$ ) for group A and group B, respectively. The real outcome at 3 years of all genoidentical allogeneic transplants (group A + group B)



**Figure 1** Outcome at 3 years of patients transplanted in Europe in 1993 for hematological malignancies from group A (2595 patients) and group B (3056 patients). Figure (a) shows DFS, (b) RI and (c) TRM. Results show that outcome between the two groups are identical reflecting the actual outcome of all patients (group A + group B).

was  $49 \pm 1\%$ ,  $29 \pm 1\%$ ,  $31 \pm 1\%$  and  $54 \pm 1\%$  for DFS, RI, TRM and OS, respectively.

For other allogeneic transplants DFS was  $32 \pm 3\%$  and  $31 \pm 3\%$  ( $P = 0.97$ ), RI  $34 \pm 5\%$  and  $34 \pm 3\%$  ( $P = 0.84$ ), TRM  $51 \pm 4\%$  and  $52 \pm 3\%$  ( $P = 0.86$ ) and OS  $37 \pm 3\%$  and  $39 \pm 3\%$  ( $P = 0.6$ ) for group A and group B, respectively. The real outcome at 3 years of all other allogeneic transplants (group A + group B) was  $31 \pm 2\%$ ,  $34 \pm 3\%$ ,  $52 \pm 2\%$  and  $38 \pm 2\%$  for DFS, RI, TRM and OS, respectively.

#### Outcome at 3 years by disease category

Table 2 shows results on DFS, RI, TRM and OS for autologous transplants, Table 3 for genotypical allogeneic transplants and Table 4 for other allogeneic transplants.

Results by disease category and by transplant modality showed no difference for outcome between group A and B.

#### Discussion

This study was undertaken to test whether the outcome of patients with hematological malignancies transplanted dur-

ing 1 year, the year 1993, reported spontaneously to the EBMT did indeed reflect the outcome of all patients transplanted during the same year. For this purpose, additional information was retrieved by solicitation. Results showed very similar Figures for both groups. The observation is important, since the large population of patients in this study allows a very high statistical power. This work has provided reassuring information that patients reported to a transplant registry are representative of all patients and are not a selected group.

A second important consequence of this study has been to produce highly reliable indicators of outcome following transplantation in various diseases, taking advantage of an optimal registry with all consecutive data reported, and a minimum follow-up of 5 years. This has been a considerable effort not only for the investigators who were assigned the task of tracking all transplants done in Europe for the year 1993, but also for all EBMT teams.

With the implementation of the new telematic network designed by the EBMT, it is foreseen that complete consecutive automatic data reporting will be routinely achieved yearly by 2002 and a search such as this will no longer be necessary. The effort has been fruitful since, by all indi-

**Table 2** Outcome at 3 years by disease category of patients with hematological malignancies treated by autologous stem cell transplantation performed in 1993 in Europe and comparison between group A and group B. Results show a similar outcome for the two groups

	<i>Non-Hodgkin's lymphoma</i>			<i>Multiple myeloma</i>			<i>Hodgkin's disease</i>			<i>Acute myeloid leukemia</i>			<i>Acute lymphoid leukemia</i>		
	A	B	P	A	B	P	A	B	P	A	B	P	A	B	P
DFS (%)	46 ± 2	48 ± 3	0.61	31 ± 5	37 ± 3	0.24	51 ± 3	56 ± 3	0.2	42 ± 3	46 ± 3	0.5	39 ± 4	37 ± 4	0.92
RI (%)	48 ± 2	46 ± 3	0.70	64 ± 6	55 ± 3	0.27	59 ± 3	36 ± 3	0.24	50 ± 4	43 ± 3	0.18	55 ± 4	56 ± 4	0.87
TRM (%)	11 ± 1	11 ± 2	0.70	13 ± 4	16 ± 3	0.68	14 ± 2	13 ± 2	0.57	14 ± 3	18 ± 2	0.35	13 ± 3	15 ± 3	0.91
OS (%)	58 ± 2	60 ± 3	0.33	50 ± 5	56 ± 3	0.12	63 ± 3	70 ± 3	0.055	51 ± 3	53 ± 3	0.67	44 ± 4	45 ± 4	0.70

**Table 3** Outcome at 3 years by disease category of patients with hematological malignancies following genoidentical allogeneic stem cell transplantation performed in 1993 in Europe and comparison of outcome between group A and group B. Results show a similar outcome for the two groups

	<i>Acute myeloid leukemia</i>			<i>Acute lymphoid leukemia</i>			<i>Myelo-dysplastic syndrome</i>			<i>Chronic myeloid leukemia</i>			<i>Multiple myeloma</i>			<i>Non-Hodgkin's lymphoma</i>			<i>Aplastic anemia</i>		
	A	B	P	A	B	P	A	B	P	A	B	P	A	B	P	A	B	P	A	B	P
DFS (%)	52 ± 3	48 ± 3	0.58	44 ± 4	42 ± 4	0.95	35 ± 7	46 ± 6	0.55	56 ± 3	50 ± 3	0.29	20 ± 7	22 ± 6	0.99	41 ± 10	43 ± 6	0.69	78 ± 5	69 ± 4	0.20
RI (%)	31 ± 3	32 ± 3	0.77	35 ± 4	42 ± 4	0.18	36 ± 8	28 ± 7	0.38	17 ± 3	23 ± 3	0.23	44 ± 14	52 ± 11	0.84	40 ± 12	29 ± 7	0.79	0	8 ± 3	0.04
TRM (%)	24 ± 3	29 ± 3	0.62	32 ± 4	27 ± 4	0.11	44 ± 9	35 ± 6	0.99	32 ± 3	34 ± 3	0.66	64 ± 14	55 ± 11	0.89	31 ± 9	39 ± 7	0.47	22 ± 5	25 ± 4	0.61
OS (%)	56 ± 3	52 ± 3	0.41	50 ± 4	48 ± 4	0.82	38 ± 7	54 ± 7	0.26	62 ± 3	57 ± 3	0.39	34 ± 8	32 ± 8	0.83	59 ± 10	45 ± 6	0.23	78 ± 5	74 ± 4	0.49

**Table 4** Outcome at 3 years by disease category of patients with hematological malignancies following other allogeneic stem cell transplantation (syngeneic, other family related and unrelated) performed in 1993 in Europe and comparison of outcome between group A and group B. Results show a similar outcome for the two groups

	<i>Acute myeloid leukemia</i>			<i>Acute lymphoid leukemia</i>			<i>Chronic myeloid leukemia</i>			<i>Aplastic anemia</i>		
	A	B	P	A	B	P	A	B	P	A	B	P
DFS (%)	27 ± 10	31 ± 6	0.56	23 ± 6	34 ± 5	0.15	39 ± 5	33 ± 5	0.47	43 ± 12	17 ± 6	0.11
RI (%)	52 ± 15	42 ± 8	0.66	50 ± 10	34 ± 6	0.26	27 ± 6	33 ± 6	0.29	14 ± 9	23 ± 15	0.62
TRM (%)	44 ± 11	45 ± 7	0.7	54 ± 7	48 ± 6	0.34	47 ± 6	50 ± 5	0.88	50 ± 13	77 ± 7	0.07
OS (%)	32 ± 10	41 ± 6	0.25	24 ± 6	38 ± 5	0.14	46 ± 5	45 ± 5	0.88	49 ± 12	23 ± 7	0.08

cators available, including the yearly EBMT caseload reports, the 5945 transplants collected for this study probably represents 93.8% of all transplants done in Europe for hematological malignancies during the year 1993. What happened to these patients provides information of potential importance not only in terms of therapeutic management, but also in terms of epidemiology and public health. Indeed, more than 50% of patients with hematological malignancies treated by hematopoietic stem cell transplantation during the year 1993 have experienced long-term survival.

This study indicates that the numerous scientific analyses that have been carried out to date on EBMT registries, which contain incomplete information, have nonetheless generated reliable information.

While this observation is reassuring, it must however be emphasized that the conclusions are from a retrospective study and that it would not support by any means that non-exhaustive collection of supposedly representative data from selected centres would constitute the bases for future

analysis. Electronic data collection aiming to pick up all transplants is the EBMT goal for the beginning of this century.

### Acknowledgements

This work was supported in part by EBMT funds, Association pour la Recherche contre le Cancer (ARC, Villejuif, France), Establisement Français des Greffes (EFG, Paris, France) and Association Claude Bernard (Paris, France).

### Appendix: Teams reporting data for this study

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