

ORIGINAL ARTICLE

Comparison of long-term outcomes after allogeneic hematopoietic stem cell transplantation from matched sibling and unrelated donors

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Long-term survivors of hematopoietic stem cell transplants remain at risk of potentially fatal complications that detract from life quality. Long-term morbidity and mortality were compared between matched recipient cohorts surviving 2 or more years and defined by donor type, HLA matched sibling donor (MSD) or volunteer unrelated donor (URD). Patients were previously entered into the prospective multicenter International Unrelated Search and Transplant Study. Thirty-nine centers provided data on 108 URD and 355 MSD recipients surviving more than 2 years. Long-term survival, performance status, chronic GvHD (c-GvHD), secondary malignancy, endocrine dysfunction, cataracts, bone necrosis and dental pathology were compared between cohorts. Twelve year survival was $77 \pm 5\%$ for the MSD and $67 \pm 11\%$ for the URD cohort ($P = 0.1$). Late death occurred in 105 of 463 recipients alive at 2 years, 73 after 355 (21%) MSD and 32 after 108 (30%) URD transplants, $P = 0.10$. Of 105 deaths, the cause was relapse in 60 and unrelated to relapse in 45 cases. Cumulative incidence of extensive c-GvHD ($P = 0.002$), cataracts ($P = 0.02$) and bone necrosis ($P = 0.02$) was higher after URD transplants. No long-term difference in endocrine dysfunction, secondary malignancy and major dental pathology was detected. This landmark study will assist physicians counseling patients pre-transplant and with their long-term care post transplant.

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Introduction

Allogeneic hematopoietic stem cell transplantation is an established therapy for hematologic malignancy with approximately 50% of patients becoming long-term survivors.^{1,2} The incidence of treatment-related mortality within 2 years is 20–30% and of disease recurrence within 2 years 10–20%.³ Patients surviving beyond 2 years remain at risk of relapse and transplant-related morbidity and mortality.^{4–6} Major late transplant-related complications are chronic GvHD (c-GvHD),⁷ second malignancy, endocrine failure, cataracts and bone necrosis.⁵ Analysis of late complications in long-term survivors is essential to optimize management and to find ways to reduce toxicity of transplant protocols.

The ideal allogeneic stem cell donor is an HLA matched sibling donor (MSD), minimizing the probability of post transplant allo-immune complications, including acute and c-GvHD.⁸ The probability of patients in the western world having a MSD within their family is about 30%. In many countries, family size is becoming smaller, reducing the number of MSD. There has been intensive worldwide activity to establish a network of volunteer unrelated donor (URD) registries,⁹ <http://www.bmdw.org/>. Approximately 10 million adult volunteer donors have been tissue typed and the numbers of transplants from URDs are rising steadily.¹⁰

The use of URDs has been associated with an increased probability of early transplant-related mortality and morbidity.⁸ In contrast, there are few data on long-term outcome. For patients with a good clinical performance

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score, the use of URD transplantation remains a curative option. Investigating the long-term outcome beyond 2 years of URD compared with MSD transplantation is therefore warranted and is the primary aim of this analysis. This is the first multicenter study of long-term quality of life, morbidity and mortality after stem cell transplantation using prospectively matched patient cohorts.

Methods

Patient selection

Between 1989 and 1992, the International Unrelated Search and Transplant (IMUST) Study Group prospectively collected data from 353 URD transplants consecutively performed at 41 transplant centers reporting to the European Group for Blood and Marrow Transplantation.¹¹ A control cohort of 724 HLA MSD transplants was accrued over the same time period. Two MSD transplants were recruited for each unrelated transplant, assuming that early post transplant death was twice as likely to occur after URD transplants.¹² The cohorts were prospectively matched for transplant center, diagnosis, patient age and stage of disease at the time of transplantation. Clinical follow-up data were requested on study forms at 3, 6 and 12 months, then annually. Interim results of the prospective cohort controlled study have been published.^{11,13}

Thirty-nine of the 41 centers contributing data to the IMUST Study participated in the current study contributing 361 MSD and 119 URD recipients surviving more than 2 years after transplantation. Two of 41 centers were not eligible having no survivors at 2 years after transplantation. Two of 39 centers were excluded because of incomplete data in 20 cases (six MSD and 14 URD transplants). All 463 long-term survivors from the remaining 37 centers were included, 355 in the MSD and 108 in the URD cohort. There were no differences in patient or transplant characteristics before and after exclusion of the two centers.

Data collection and definitions in current study

Thirty-seven centers completed a study questionnaire on included patients requesting details of survival, date of last follow-up, Karnofsky status as assessed by the physicians (good 90–100; poor less than 90), c-GvHD, second malignancy, bone necrosis, cataracts and endocrine failure. Endocrine failure was defined as biochemical and clinical evidence for one or more of the following, gonadal failure, thyroid insufficiency, growth hormone deficiency or diabetes mellitus. Primary data were recorded locally utilizing the participating centers own protocols. Severity of c-GvHD was assessed using published criteria.¹⁴ Second malignancies were documented from pathology reports; diagnosis of endocrine failure was based on clinical observation and biochemistry, bone necrosis on radiology and magnetic resonance imaging and cataracts on ophthalmologic examination. One study investigator validated data by direct contact with the centers and reference to the IMUST Study and European Group for Blood and Marrow Transplantation (EBMT) databases. Institutional review boards at individual centers approved the data

collection and all individuals provided informed consent according to the Declaration of Helsinki.

Patient and transplant characteristics

Patient and transplant characteristics are summarized in Table 1. Status and date of last follow-up was from April 2004. Median follow-up of recipients of 355 MSD and 108 URD transplants alive at 2 years was 10 years (range 3–14 years) and 10 years (range 7–14 years), respectively. Only 10% of all recipients were followed for less than 8 years. Most patients were transplanted for hematologic malignancy. There were no significant differences in the distribution of the main diagnostic categories, patient age and patient gender between the two cohorts. Typing of HLA-A, -B and -DR alleles was carried out using serological methods as described previously.¹¹ In the URD cohort, 99 pairs were HLA matched and nine mismatched. TBI was utilized at equal frequency in the two cohorts. Patients with hematologic malignancy either received 10 Gy unfractionated or 12 Gy fractionated TBI with no difference in the utilization of each TBI regimen in the two cohorts. Donor T-cell depletion to prevent GvHD was used less frequently in MSD transplants (Table 1). All patients received bone marrow donations, and all those with hematological malignancy received myeloablative conditioning treatment.

Statistical analysis

Events occurring after 2 years post transplant were analyzed, as reported by others.⁶ The Kaplan–Meier estimator was used to assess the probability of survival.¹⁵ Cumulative incidence rates and their 95% confidence intervals (CIs)¹⁶ were used to estimate c-GvHD, second

Table 1 Characteristics of patients surviving 2 or more years post transplant related to donor type

	MSD n = 355	URD n = 108	P-value
<i>Diagnosis</i>	<i>n (%)</i>	<i>n (%)</i>	0.33
Acute leukemia	123 (35)	36 (33)	
Chronic leukemia	162 (47)	57 (53)	
MPS/MDS	12 (3)	3 (3)	
NHL/MM	21 (5)	1 (1)	
Inherited disorder	10 (3)	4 (4)	
Acquired aplastic anemia	27 (7)	7 (6)	
Median age, years (range)	30 (1–57)	27 (1–48)	0.6
Gender, M/F	200/155	70/38	0.12
<i>HLA donor–recipient match^a</i>			NA
HLA match	355	99	
HLA mismatch	0	9	
TBI conditioning ^b , yes/no	259/96	85/23	0.23
T-cell depletion ^c , yes/no	68/287	33/75	0.01
Years follow-up (range)	10 (3–14)	10 (7–14)	NA

Abbreviations: F = female; M = male; MPS/MDS = myeloproliferative syndrome/myelodysplastic syndrome; MSD = matched sibling donor; NA = not available; NHL/MM = non-Hodgkin's lymphoma/multiple myeloma; URD = volunteer unrelated donor.

^aSerological typing of HLA-A, -B, -DR loci.

^bTotal body irradiation pre-transplant conditioning therapy.

^cT-cell depletion of donor marrow.

malignancies, endocrine failure, bone necrosis and cataracts. The log-rank test was used to compare groups. The Cox proportional hazards regression model was used to independently assess the impact of donor type on outcomes after adjusting for other covariates. Proportionality was tested using time-dependent covariates and non-proportionality was dealt with by modeling time varying effects.¹⁷ Frequent outcomes were subjected to multivariate analysis, for example, death and c-GvHD. All types of endocrine failure were combined as a single outcome allowing multivariate analysis.⁶ Events reported rarely, for example, bone necrosis, were only analyzed by univariate methods.

Results

Survival and cause of death

The probability of 12-year survival for all patients alive 2 years or more post transplant was $75 \pm 5\%$, $77 \pm 5\%$ for the MSD and $67 \pm 11\%$ for the URD cohort, $P = 0.1$ (Figure 1). Deaths continued to occur in both cohorts with 105 deaths among the 463 patients studied. Seventy-three deaths occurred after 355 MSD and 32 after 108 URD transplants. Relapse was the cause of death in 42 of 74 (57%) patients from the MSD cohort and in 18 of 31 (58%) patients from the URD cohort ($P = 1.00$). Death was due to non-relapse mortality in 45 cases. Nineteen of the 339 survivors were lost to follow-up, although 15 of the 19 were followed for more than 5 years.

Late effects and performance status

The cumulative incidence at 12 years of extensive c-GvHD, cataract formation and bone necrosis was significantly higher in the long-term survivors of the URD compared with the MSD cohort (Table 2). In contrast, no difference in cumulative incidence of endocrine dysfunction, secondary malignancy and major dental pathology was detected (Table 2). A similar proportion of patients with a poor Karnofsky performance score of less than 90% was observed in the long-term survivors in the two cohorts, eight of 70 (11%) patients in the URD compared with 20 of 240 (8%) patients in the MSD cohort, 48 with missing data (13%), $P = 0.47$.

Donor type and c-GvHD

C-GvHD was reported in 221 of 463 (48%) patients and the cumulative incidence of extensive c-GvHD is shown in Table 2. The probability of survival in patients without c-GvHD was similar in the MSD and URD cohorts, $P = 0.12$ (Figure 2a). Survival in the presence of limited c-GvHD was also similar comparing the two cohorts (Figure 2b). Patients with extensive c-GvHD in both cohorts had a reduced probability of survival (Figure 2c). Multivariate analysis of factors independently predicting survival is shown in Table 3.

Donor type and secondary malignancy

The reported incidence of secondary malignancy was low in both cohorts. Twenty-five patients developed 26 secondary malignancies, 17 of 355 patients in the MSD and 8 of

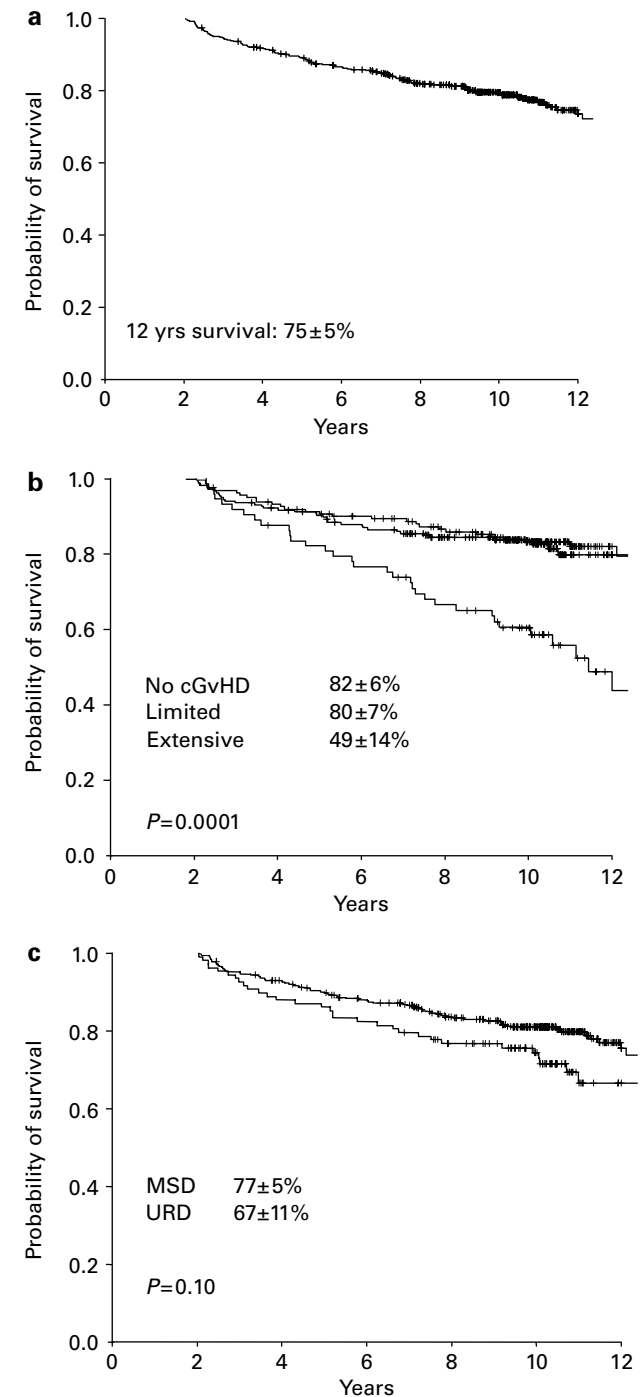


Figure 1 Probability of late survival 2 and more years after allogeneic stem cell transplantation. Figure shows the probability of late survival 2 or more years after allogeneic stem cell transplantation. (a) The probability of survival in all patients. (b) The probability of survival is significantly worse in patients with extensive c-GvHD, $49 \pm 14\%$, compared with those with no c-GvHD, $82 \pm 6\%$, or limited disease, $80 \pm 7\%$, $P = 0.0001$. (c) A nonsignificant trend toward worse survival in the URD cohort, $67 \pm 11\%$, compared with the MSD cohort, $77 \pm 5\%$, $P = 0.10$.

108 patients in the URD cohort. The cumulative incidence of secondary malignancy is shown in Table 2 and was associated with extensive c-GvHD, 15% (CI 7–34), compared with 4% (CI 1–14) for limited and 2%

Table 2 Cumulative incidence of late effects related to donor type at 12 years after allogeneic stem cell transplantation

	MSD % (CI) ^a	URD % (CI)	P-value
Extensive c-GvHD ^b	30 (22–42)	49 (44–55)	0.002
Cataract formation	28 (24–34)	43 (33–57)	0.02
Endocrine failure	29 (23–35)	28 (19–40)	0.8
Bone necrosis	3 (2–6)	9 (4–17)	0.02
Second malignancy	5 (3–11)	4 (2–10)	0.75
Major dental pathology	10 (6–17)	5 (2–12)	0.45

Abbreviations: MSD = matched sibling donor; URD = volunteer unrelated donor.

^a95% confidence interval.

^bExtensive c-GvHD.

(CI 0–5%) for absent disease, $P = 0.0001$. The commonest malignancy was squamous cell carcinoma of the tongue or oral cavity with nine cases reported. Breast carcinoma was reported in three cases, osteosarcoma in three, gastrointestinal carcinoma in two, central nervous system malignancy in two and one case each of secondary leukemia, non-Hodgkin's lymphoma, thyroid cancer and basal cell carcinoma. Unspecified malignancy was reported in two cases. Twelve of the 25 patients died from malignancy.

Donor type and endocrine failure

Endocrine failure was reported in 114 of 463 of the late survivors, 82 of 355 patients in the MSD and 27 of 108 patients in the URD cohort. The cumulative incidence of endocrine is shown in Table 2 and was significantly higher in female patients, 41% (CI 34–50), compared with male patients, 19% (CI 14–26), $P = <0.0001$. By 12 years post transplant, the cumulative incidence of endocrine failure in children under 10 years had risen to 59% (CI 47–79) compared with 23% (CI 18–29) in older recipients, $P = <0.0001$. These findings were confirmed by multivariate analysis (Table 4).

Donor type and cataracts

Cataracts were reported in a total of 135 cases, 95 patients in the MSD and 40 patients in the URD cohort. The cumulative incidence of cataracts is shown in Table 2. Patients treated with TBI had a higher cumulative incidence of cataract formation at 12 years, 39% (CI 34–46), compared with those who received none, 11% (CI 5–22%), $P = <0.0001$. In multivariate analysis, TBI and donor type remained independent predictors of cataract formation, relative risks 5.5 (CI 2.7–11.2) and 1.5 (CI 1.0–2.3), respectively, $P = 0.03$.

Donor type and bone necrosis

Bone necrosis was reported infrequently in late survivors. Ten patients were reported in the MSD and 13 patients in the URD cohort. The cumulative incidence is shown in Table 2, and was significantly higher in patients with extensive c-GvHD, 11% (CI 6–23), compared with limited, 7% (CI 4–12), or no c-GvHD, 1% (CI 0–4), $P = 0.0002$.

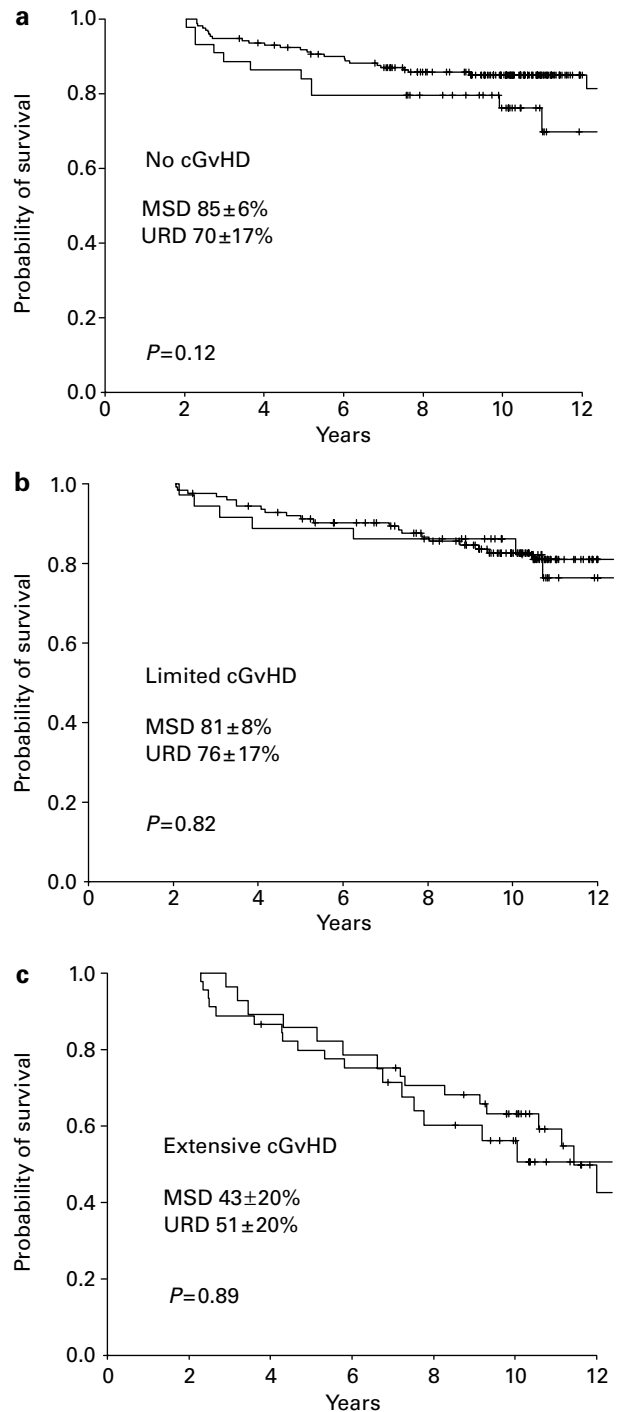


Figure 2 Probability of late survival by donor type and severity of c-GvHD. Figure shows the probability of late survival in relation to donor type and c-GvHD. There was no significant difference in survival between URD and MSD transplant recipients with either extensive or limited c-GvHD. However, in patients without c-GvHD there was a nonsignificant trend toward worse survival in recipients of URD transplants, $70 \pm 17\%$, compared to recipients of MSD transplants, $85 \pm 6\%$, $P = 0.12$.

Discussion

This is the first multicenter study of late morbidity and mortality in prospectively matched cohorts comparing

Table 3 Multivariate analysis of survival of patients alive 2 years after allogeneic stem cell transplantation

Variable	Relative risk	95% CI	P-value
<i>Donor type</i>			
MSD	1.0		
URD	1.4	0.9–2.2	0.14
<i>Recipient age (years)</i>			
<20	1.0		
20–40	1.9	1.1–3.4	0.02
>40	2.4	1.3–4.6	0.007
<i>c-GvHD^a</i>			
None	1.0		
Limited	0.8	0.5–1.4	0.8
Extensive	2.3	1.4–3.7	0.01

Abbreviations: CI = confidence interval; MSD = matched sibling donor; URD = volunteer unrelated donor.

^aExtensive c-GvHD.

Table 4 Multivariate analysis of endocrine failure after allogeneic SCT

Variable	Relative risk	95% CI ^a	P-value
<i>Donor type</i>			
URD	0.83	0.51–1.34	0.45
<i>Female gender</i>			
Events before 1 year	21.1	5.0–89	0.0001
Events after 1 year	1.6	1.0–2.5	0.06
<i>Age less than 10 years</i>			
Events before 2 years	0.2	0.0–0.8	0.03
Events after 2 years	8.6	5.0–15	0.0001
T-cell depletion	3.0	2.0–4.5	0.0001

Abbreviations: CI = confidence interval; URD = volunteer unrelated donor.

^a95% confidence interval.

MSD and URD transplants. URDs were also associated with a significantly increased cumulative incidence of extensive c-GvHD, cataract formation and bone necrosis at 12 years post transplant. There was a trend toward worse survival in the URD compared with the MSD cohort.

Published IMUST Study data showed the deleterious effect of donor type on short-term transplant outcomes.^{11,13} The probability of survival after 400 days was worse in the unrelated compared with the MSD cohort, $P = <0.001$. Multivariate analysis confirmed that donor type was a powerful independent predictor of early survival. There was also a significantly higher probability of Grade II–IV acute GvHD in the URD cohort, $P = 0.009$. The current analysis shows the continued effect of donor type on the incidence of GvHD in the long term. The cumulative incidence at 12 years of extensive c-GvHD was 49% (CI 44–55) in the URD compared with 30% (CI 22–42) in the MSD cohort, $P = 0.002$.

The higher incidence of extensive c-GvHD in the URD cohort may in part be due to undetected HLA mismatches in the 99 ‘matched’ URD-recipient pairs¹⁸ as HLA typing of HLA-A, -B and -DR loci was by serology.¹¹ In addition,

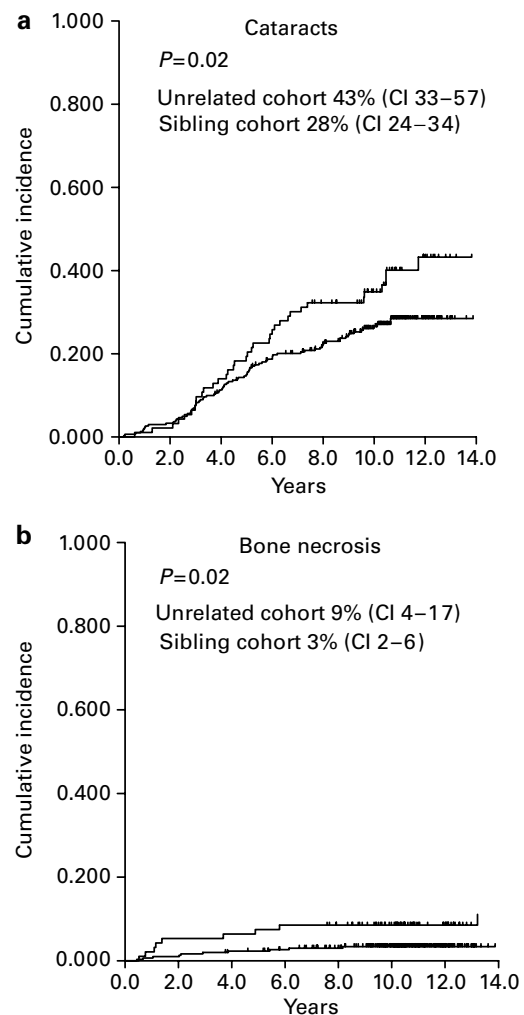


Figure 3 Cumulative incidence of cataracts and bone necrosis by donor type 12 years after allogeneic stem cell transplantation. Figure shows the cumulative incidence of cataract and bone necrosis in late survivors 12 years after allogeneic stem cell transplantation. (a) A significantly higher cumulative incidence of cataracts in the URD cohort, 43% (CI 33–57), compared with the MSD cohort, 28% (CI 24–34), $P = 0.02$. (b) The cumulative incidence of bone necrosis is significantly higher in the URD cohort, 9% (CI 4–17), compared with the MSD cohort, 3% (CI 2–6), $P = 0.02$.

nine of 108 pairs were overtly mismatched. High resolution DNA typing of donors and recipients for HLA-A, -B, -C, -DRB1 and -DQB1 loci^{19,20} has since been associated with improved survival and reduced GvHD after URD transplantation.²¹ In contrast, some investigators have since observed a low incidence of GvHD after T-cell depleted HLA mismatched transplants.²²

Cataracts detract from quality of life and were more frequent in the URD cohort (Table 2 and Figure 3a). The mainstay of therapy for c-GvHD is prolonged corticosteroid therapy,^{14,23,24} suggesting that corticosteroids were associated with the significantly higher incidence of cataracts in the URD cohort.⁵ It is unlikely that extensive c-GvHD directly contributed to cataract formation, as the lens is avascular. An association between TBI and cataract formation was found in this study as documented elsewhere.²⁵ Patients with hematologic malignancy either

received 10 Gy unfractionated or 12 Gy fractionated TBI. More detailed information about TBI regimens was not collected; however, it is likely that recipients of URD transplantation received more intensive TBI regimens as significantly more URD recipients received T-cell depleted grafts (Table 1).

We observed a higher incidence of bone necrosis in the URD compared with the MSD cohort (Figure 3b). The cumulative incidence of bone necrosis at 12 years reached 11% in patients affected by extensive c-GvHD, and was more frequent in the URD cohort (Figure 3). C-GvHD of bone is not a recognized condition, but it is likely that prolonged therapy with corticosteroids increased the probability of bone necrosis.²⁶ Many patients with bone necrosis have a poor quality of life and around 50% of affected patients require joint replacement therapy.²⁷

No association between secondary malignancy and donor type was found in the current study (Table 2). However, extensive c-GvHD was associated with secondary malignancy, as reported by others.^{6,28} Failure to detect a difference in the incidence of secondary malignancy between the cohorts may be due to the low incidence of malignancy combined with the relatively small overall number of patients studied. The cumulative incidence of second malignancies is known to continue to rise beyond 10 years compared with the age-matched general population;⁶ therefore, a difference may be identified with longer follow-up.

Endocrine failure was frequently reported in both MSD and URD cohorts (Table 2), with no difference in the cumulative incidence at 12 years, $P=0.8$. Previous studies have emphasized the female predominance of endocrine failure after transplantation mainly owing to ovarian failure secondary to irradiation and busulfan administration.²⁹ We support this observation by showing endocrine failure in female subjects is usually diagnosed in the first post transplant year (Table 4). We did not evaluate late recovery of ovarian function during this study. It has been shown elsewhere that recovery of reproductive function after allogeneic stem cell transplantation is rare apart from in children and patients transplanted for severe aplastic anemia.^{30,31} This analysis demonstrated that young age is an important factor predicting endocrine failure (Table 4). Most episodes of endocrine failure in children were late (Table 4). The likely explanation is that growth retardation can only be diagnosed after a latent period. The observation that endocrine failure was found to be associated with the use of T-cell depletion, Table 4, is probably due to the well-known association between the use of T-cell depleted grafts and intensive TBI regimens.

The current analysis is focused on differences in long-term outcome associated with donor type analyzing events occurring after 2 years post transplant. HLA typing, transplant protocols and supportive care have improved and the median age of adult transplant recipients has increased since the early 1990s. However, the observations made in this study remain highly relevant today. The use of prospectively matched cohorts facilitated detection of differences in long-term follow-up relating to donor type that still has relevance in the current transplant era. Despite prospective matching, a limitation of this study is the relatively small number of eligible patients. Therefore,

results of analysis of unusual events such as secondary malignancy have been interpreted with caution. Another important caveat is that additional studies will become necessary in the future to evaluate the impact of donor type on long-term outcome after URD transplants where donor selection has been performed using high resolution DNA-based HLA typing techniques.

This study is of value to patients and physicians who care for long-term survivors in the community after discharge from transplant units. The analysis also provides background information for patients and physicians when an HLA-identical MSD is not available and the choice between an URD transplant and alternative therapy has to be made.

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Appendix

The following centers participated in the Study of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation:

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