Bone Marrow Transplantation (2003) 31, 667–678

www.nature.com/bmt

Lymphoma

An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation

AJ Peniket, MC Ruiz de Elvira, G Taghipour, C Cordonnier, E Gluckman, T de Witte, G Santini, D Blaise, H Greinix, A Ferrant, J Cornelissen, N Schmitz and AH Goldstone on behalf of the European Bone Marrow Transplantation (EBMT) Lymphoma Registry

Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, Oxford, UK

Summary:

The role of allogeneic bone marrow transplantation in lymphoma remains uncertain. We have analyzed 1185 allogeneic transplants for lymphoma reported to the EBMT registry between 1982 and 1998 and compared the results with those of 14 687 autologous procedures performed over the same period. Patients receiving allogeneic transplants were subdivided according to histology: low-grade non-Hodgkin's lymphoma (NHL) 231 patients; intermediate-grade NHL 147 patients; high-grade NHL 255 patients; lymphoblastic NHL 314 patients; Burkitt's lymphoma 71 patients; and Hodgkin's disease 167 patients. These patients received allogeneic transplants as their first transplant procedure. Actuarial overall survival (OS) at 4 years from transplantation was: low-grade NHL 51.1%; intermediate-grade NHL 38.3%; high-grade NHL 41.2%; lymphoblastic lymphoma 42.0% years; Burkitt's lymphoma 37.1%; and Hodgkin's disease 24.7% years. These outcomes are relatively poor because of the high procedure-related mortality associated with these procedures, particularly in patients with Hodgkin's disease (51.7% actuarial procedure-related mortality at 4 years). Multivariate analysis showed that for all lymphomas apart from Hodgkin's disease, status at transplantation significantly affected outcome. A matched analysis was performed: for all categories of lymphoma, OS was better for autologous than for allogeneic transplantation. Relapse rate was better in the allogeneic group for low-, intermediate- and high-grade, and lymphoblastic NHL. It was equivalent for Burkitt's lymphoma and worse in the allogeneic group for Hodgkin's disease. Allogeneic transplantation appears to be superior to autologous procedures in terms of producing a lower relapse rate. The toxicity of allogeneic procedures must however be reduced before this translates into an improvement in OS.

Correspondence: Dr AJ Peniket, Nuffield Department of Clinical Laboratory Sciences, Room 4709, John Radcliffe Hospital, Oxford OX3 9DU, UK
Received 3 January 2002; accepted 1 November 2002

Bone Marrow Transplantation (2003) **31,** 667–678. doi:10.1038/sj.bmt.1703891
Keywords: allogeneic stem cell transplant; lymphoma

The use of high-dose therapy and autologous hematopoietic stem cell transplantation has become widespread in patients with lymphoma.[1–5] The indications for and the use of allogeneic stem cell transplantation in these patients remain poorly defined. The relatively successful use of autologous procedures has perhaps precluded widespread use of allografting such as has occurred in acute and chronic leukemia. The use of allogeneic stem cell transplantation has two main theoretical justifications. Firstly, the problems of tumor contamination from reinfused autologous bone marrow are avoided since the allogeneic hematopoietic cells are tumor-free.[6] Secondly, it has been postulated that a graft-versus-lymphoma effect (analogous to graft-versus-leukemia effect) may be of direct therapeutic value.[7,8] The major practical problem with allogeneic transplantation is the increased treatment-related mortality in comparison to autologous transplantation.[9,10]

We here report the EBMT experience with allogeneic stem cell transplantation, principally to address two issues: is the relapse rate lower than expected with allogeneic transplantation; and do the problems with these procedures outweigh the advantages in terms of overall survival (OS)?

Subjects and methodology

The first allogeneic transplant for lymphoma reported to the EBMT was performed in 1982. We used this year as the starting point for the study. For the period between 1982 and 1998, the EBMT Lymphoma Registry held 18 908 procedures, of which 18 593 were first transplants. Of these first transplant procedures, 1483 were allogeneic transplants. The analysis was restricted to the 1185 patients receiving allogeneic stem cell transplantation as a first transplant who could be classified according to histological subtypes derived from the Working Formulation.

Patients were divided into six groups according to the histological subtype reported by the referring center: (1) Low-grade non-Hodgkin's lymphoma (NHL); (2) Intermediate-grade NHL; (3) High-grade NHL (immunoblastic subtypes); (4) Lymphoblastic lymphoma; (5) Burkitt's lymphoma; and (6) Hodgkin's disease. This histological classification followed the Working Formulation, which was the principal classification system in use during the long period under study.[11] Reclassification of these lymphomas according to the REAL system was not practical given the large number of cases involved.[12] Patient characteristics at diagnosis and transplantation were compared for the autologous and allogeneic populations using univariate and multivariate analyses. The aim of these analyses was to detect imbalances in patients' characteristics at diagnosis and transplant between the autologous and allogeneic groups which could affect outcome independently of the allogeneic or autologous nature of the procedure.

Study of outcome using controlled matched subsets

The information obtained from the first stage of the analyses was used to select the matching variables and find matches for the allogeneic population within the autologous population. The possible difference in outcome of the autologous *vs* the allogeneic first transplants was analyzed in a controlled matched study.

Statistical techniques

Comparisons between groups were carried out using *t*-tests or Mann–Whitney *U*-tests as necessary. The distribution of a variable in the different groups was analyzed using contingency tables. Prognostic factors were studied with the Cox regression model. The proportional hazards assumption was tested with standard graphical methods, and stratification was used when lack of proportionality of the hazards was evident.

In the first instance all analyses were run on patients for whom all possible prognostic variables were reported to the EBMT. If variables were found to be grossly nonsignificant, they were dropped from the analyses, allowing more patients to enter the model. To check that patients left out of the final analysis because of missing data in at least one prognostic factor were not in other ways different from the analyzable population, the outcome measurements, progress-free survival (PFS), relapse rate, and procedure-related mortality (PRM) of these groups were compared with the equivalent groups of patients used in the analysis. No significant differences were found, indicating that the loss of a subset of the population because of missing data was not likely to have biased the results.

Statistical analyses were performed using Stata. Matching was carried out using a program developed for that purpose by Dr Walter Gregory. The program matched a number of variables according to rules provided by the user, which allowed for different variables to be matched with different accuracy and in a pre-established order. For example, status at transplantation was selected as the first variable to be matched and the match to be exact; age, however, was not matched exactly but within a range of ± 5 years. After matching was been accomplished, the program provided information on degree of matching and number of perfect matches found. The files used for matching access the records in a random order avoiding possible bias due to the underlying structure of the existing sorting order. Event–time distributions were estimated using the method of Kaplan and Meier and log-rank tests were used to detect differences in event–time distributions between the allogeneic and autologous populations in the matched analysis.

Variables

Within each histological subcategory patients were analyzed according to the following characteristics at diagnosis: age, sex, stage, presence or absence of B-symptoms, and bone marrow (BM)/CNS involvement. A record of the diagnostic LDH was available in relatively few patients and so was not included in the analysis. The patients were also analyzed in terms of the characteristics at transplantation: age, BM/CNS involvement, largest lymphoma mass at transplant, number of first line treatments, disease status at transplantation, and year of transplantation.

Disease status at transplantation was classified as follows: complete remission (CR) (total resolution of all active disease areas in response to treatment); chemosensitive (at least a 50% reduction in the cross-sectional area of nodal regions on CT scanning following chemotherapy prior to the transplantation procedure), and chemoresistant (failure to meet the criteria for chemosensitivity following chemotherapy).

Bone marrow donors were classified as HLA-identical sibling, monozygotic identical twin, HLA-identical related, HLA-identical unrelated, HLA-nonidentical related, and HLA-nonidentical unrelated.

Other information used in the analyses were the details of preparative and supportive therapy, type of conditioning treatment including total body irradiation (TBI), use of T-cell depletion, presence and grade of acute graft-versus-host disease (aGvHD), and cause of death.

The major end points of analysis were OS, PFS, and time to relapse after transplantation. OS was defined as the time from transplantation until death from any cause. PFS was defined as the time from the day of transplantation until disease progression or death from any cause. Time to relapse was defined as time to disease progression with deaths without relapse being censored. The time to procedure-related mortality was defined as the time from the day of transplantation to death from a cause other than disease progression.

Results

Patient characteristics at diagnosis and transplantation of the allogeneic population

During the study period, the number of allogeneic transplants performed according to histological subtype were as follows: low-grade NHL 231 patients; intermediate-grade NHL 147 patients; high-grade NHL 255 patients; lymphoblastic NHL 314 patients; Burkitt's lymphoma 71 patients; and Hodgkin's disease 167 patients. The characteristics of these patients at the time of diagnosis are outlined in Table 1. Patients with low- and intermediate-grade NHL tended to be older (median age 39.1 and 35.7 years, respectively) than those in the other four categories.

The majority of patients proceeding to allograft presented with clinically advanced lymphoma. In all, 77.2% of patients with Hodgkin's disease were of Stage III or IV at diagnosis. The percentage affected within the other categories was even higher: 79.1% Burkitt's; 81.7% lymphoblastic lymphoma; 86.3% intermediate-grade NHL; 79.3% high-grade NHL; and 90.7% low-grade lymphoma. Bone marrow involvement was most commonly reported at diagnosis in patients with low-grade disease (67.7%), although it occurred within each subcategory of NHL in more than 40% of patients. Only 26.2% of allograft patients with Hodgkin's disease had bone marrow involvement at diagnosis. CNS involvement was detected in 12.0% of lymphoblastic, 12.2% of high-grade, and 15.6% of Burkitt's lymphoma patients. More male patients than female patients were transplanted within each subtype.

Characteristics at the time of transplantation are outlined in Table 2. Patients with lymphoblastic lymphoma and Burkitt's lymphoma were, in the majority of cases, transplanted in complete remission (73.8% of lymphoblastic patients and 63.1% of Burkitt's patients). Relatively few patients with low-grade lymphoma (20.8%) were transplanted in CR. The Hodgkin's disease cohort includes the highest proportion (42.4%) of patients with chemoresistant disease. Within each histological subcategory, more than 81% of all donors were HLA-identical siblings (see Table 2). A total of 3.4% of all donors were syngeneic, although none of this type was reported to the Registry in patients with Burkitt's lymphoma.

Multivariate analysis of prognostic factors affecting outcome in the allogeneic population

Patient characteristics and disease status at diagnosis and transplant were used to determine their possible effect on outcome measurements using multivariate analysis. In all types of lymphoma excluding Hodgkin's, status at transplant (classified as 1st CR, chemosensitive and chemoresistant) – had a significant effect on OS (Table 3). The mass at transplant significantly affected OS in lymphoblastic lymphoma. For Hodgkin's disease, lymph node involvement at transplant and lymphoma mass size at transplant were the most important factors to affect OS.

Relapse rate was also affected by status at transplant in most types of lymphoma, including Hodgkin's disease, but excluding low-grade lymphoma. Other factors, including age, also influenced relapse rate (see Table 3). This multivariate analysis also included the year of transplant as a variable for examination (to assess whether there was a detectable improvement in outcome in recent years): this was not found to affect the outcome significantly.

Table 1 Patients receiving allogeneic transplants: characteristics at diagnosis

	Low-grade NHL	*Intermediate-grade NHL*	*High-grade NHL*	*Lymphoblastic*	*Burkitt's*	*Hodgkin's*
Number of patients	231	147	255	314	71	167
Age (years)						
Median	39.1	35.7	27.15	22.7	22.6	24.1
Range	19.4–66.1	6.0–73.6	2.4–60.5	1.9–56.0	4.8–48.0	7.1–57.1
Sex						
Male	143 (62.7)	84 (57.5)	169 (66.5)	229 (72.9)	55 (71.4)	92 (56.1)
Female	85 (37.3)	62 (42.5)	85 (33.5)	85 (27.1)	16 (20.8)	72 (43.9)
Missing	3	1	1	0	0	3
Stage						
I+II	14 (9.3)	13 (13.7)	35 (20.7)	37 (18.3)	9 (20.9)	21 (22.8)
III+IV	137 (90.7)	82 (86.3)	134 (79.3)	165 (81.7)	34 (79.1)	71 (77.2)
Missing	80	52	86	112	28	75
B-symptoms						
Absent	107 (80.4)	68 (80.0)	122 (69.7)	143 (76.9)	29 (69.0)	42 (46.7)
Present	26 (19.6)	17 (20.0)	53 (30.3)	43 (23.1)	13 (31.0)	48 (53.3)
Missing	98	62	80	128	29	77
BM involvement						
Yes	90 (67.7)	38 (46.3)	69 (42.9)	90 (52.0)	22 (59.5)	21 (26.2)
No	43 (32.3)	44 (53.7)	92 (57.1)	83 (48.0)	15 (40.5)	59 (73.7)
Missing	98	65	94	141	34	87
CNS involvement						
Yes	1 (1.0)	1 (1.4)	18 (12.2)	18 (12.0)	5 (15.6)	0 (0.0)
No	100 (99.0)	72 (98.6)	129 (87.8)	132 (88.0)	27 (84.4)	78 (100.0)
Missing	130	74	108	164	39	89

Parentheses indicate percentages of known values only.

Table 2 Patients receiving allogeneic transplants: characteristics at transplantation

	Low-grade NHL	*Intermediate-grade NHL*	*High-grade NHL*	*Lymphoblastic*	*Burkitt's*	*Hodgkin's*
Age (years)						
Median	42.1	37.7	28.5	23.5	22.9	28.0
Range	21.7–68.0	11.8–74.7	3.5–61.1	1.9–56.9	5.5–48.4	12.0–60.3
Year of transplant						
<1989	11 (4.7)	14 (9.5)	58 (22.7)	60 (19.1)	19 (26.8)	31 (18.6)
1989–90	22 (9.5)	23 (15.6)	40 (15.7)	33 (10.5)	8 (11.3)	19 (11.4)
1991–92	21 (9.1)	19 (12.9)	32 (12.6)	73 (23.2)	12 (16.9)	22 (13.2)
1993	26 (11.3)	15 (10.2)	23 (9.0)	27 (8.6)	5 (7.0)	11 (6.6)
1994	29 (12.6)	19 (12.9)	20 (7.8)	31 (9.9)	6 (8.4)	21 (12.6)
1995	36 (15.6)	17 (11.6)	29 (11.4)	29 (9.2)	4 (5.6)	12 (7.2)
1996	39 (16.9)	18 (12.2)	29 (11.4)	32 (10.2)	10 (14.1)	20 (12.0)
1997–98	47 (20.3)	22 (15.0)	24 (9.4)	29 (9.2)	7 (9.9)	31 (18.6)
Missing	0	0	0	0	0	0
Status at transplant						
1st CR	22 (10.4)	21 (15.4)	53 (22.7)	113 (38.1)	25 (38.5)	7 (5.0)
CR>1	22 (10.4)	24 (17.6)	72 (30.9)	106 (35.7)	16 (24.6)	30 (21.6)
Chemosensitive	126 (59.4)	49 (36.1)	65 (27.9)	42 (13.1)	11 (17.0)	43 (30.9)
Chemoresistant	42 (19.8)	42 (30.9)	43 (18.5)	36 (12.1)	13 (20.0)	59 (42.4)
Missing	19	11	22	17	6	28
Donor type						
Syngeneic	8 (3.6)	10 (6.9)	9 (3.7)	5 (1.6)	0 (0.0)	7 (4.5)
Identical sibling	189 (84.0)	119 (82.6)	211 (86.5)	268 (86.7)	62 (88.6)	128 (81.5)
Matched related	19 (8.7)	8 (5.6)	9 (3.7)	11 (3.6)	1 (1.4)	6 (3.8)
Matched unrelated	5 (2.2)	1 (0.7)	7 (2.9)	15 (4.9)	3 (4.3)	4 (2.6)
Unmatched related	3 (1.3)	6 (4.2)	7 (2.9)	8 (2.6)	4 (5.7)	11 (7.0)
Unmatched unrelated	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.7)	0 (0.0)	1 (0.6)
Missing	6	3	11	5	1	10
Mass at transplant						
No mass (in CR)	44 (31.0)	45 (45.0)	125 (66.8)	219 (86.2)	41 (78.8)	37 (44.6)
<5 cm	56 (39.4)	29 (29.0)	26 (13.9)	11 (4.3)	4 (7.7)	28 (33.7)
5–10 cm	8 (5.6)	12 (12.0)	9 (4.8)	3 (1.2)	1 (1.9)	7 (8.4)
>10 cm	5 (3.5)	2 (2.0)	4 (2.1)	3 (1.2)	2 (3.8)	3 (3.6)
BM/blood/CNS involvement	29 (20.4)	12 (12.0)	23 (12.3)	18 (7.1)	4 (7.7)	8 (9.6)
Missing	89	47	68	60	19	84

Parentheses indicate percentages of known values only.

Graft-versus-host disease

An analysis on a possible relation between a decreased relapse aGvHD was performed by including the absence or presence – and level – of aGvHD in the multivariate analysis. This analysis is preliminary since it was performed on a smaller subset of the population for which we had reliable information on aGvHD manifestation. The data available on chronic GvHD were insufficient to permit a similar analysis for this condition.

It was found that high levels (3 and 4) of aGvHD had a deleterious effect on OS ($n=163$, HR=1.59, 95% CI: 1.08–2.33) and no effect on relapse rate, while low levels (1 and 2) of aGvHD, as opposed to the absence of aGvHD, had no effect on either outcome for low-grade NHL. A low level of aGvHD was associated with improved OS ($n=87$, HR=0.48, 95% CI: 0.26–0.86) and all levels of aGvHD were associated with a decrease in the relapse rate ($n=100$, HR=0.38, 95% CI: 0.18–0.84) for intermediate-grade NHL. High levels of aGvHD had a deleterious effect on OS ($n=213$, HR=1.36, 95% CI: 1.05–1.77), but were associated with improved relapse rate (HR=0.50, 95% CI: 0.39–0.91), for lymphoblastic lymphoma. For high-grade NHL, Burkitt's or Hodgkin's disease, no effect of aGvHD was seen, although a trend for low levels of aGvHD to improve OS was noted in high-grade NHL ($P=0.068$) and Hodgkin's ($P=0.085$).

Overall survival

Median OS from the date of transplant for this allogeneic population was as follows: low-grade NHL 5 years; intermediate-, high-grade NHL and lymphoblastic lymphoma 1 year; Burkitt's lymphoma 4.7. months; and Hodgkin's disease 6.8 months. Actuarial OS at 4 years was: low-grade NHL 51.1%; intermediate-grade NHL 38.3%; high-grade NHL 41.2%; lymphoblastic lymphoma 42.0% years; Burkitt's lymphoma 37.1%; and Hodgkin's disease 24.7% years.

Progression-free survival

Median PFS from the date of transplant for this allogeneic population was: low-grade NHL 1.7 years; intermediate-

Table 3 Patients receiving allogeneic transplants: multivariate analysis

Factors with a significant prognostic effect on outcome measurements	*Overall survival*			*Relapse rate*		
	Hazard ratio	*95% CI*	P-*value (one way)*	*Hazard ratio*	*95% CI*	*P-value (one way)*
Low-grade NHL						
Status at transplant	2.05	1.40–3.20	<0.001	—	—	—
Age at transplant	—	—	—	1.61	10.5–2.46	<0.03
Intermediate-grade NHL						
Status at transplant	1.47	1.0– 2.15	<0.05	2.21	1.21–4.02	<0.01
Age at diagnosis	—	—	—	5.36	2.18–13.15	<0.001
Age at transplant	—	—	—	0.25	0.11–0.57	<0.001
High-grade NHL						
Status at transplant	1.54	1.10–2.16	<0.02	3.14	2.01–4.90	<0.001
Lymphoblastic						
Status at transplant	1.97	1.40–2.78	<0.001	2.64	1.39–5.03	<0.01
Mass at transplant	1.27	1.09–1.48	<0.01	3.01	1.62–5.61	<0.001
Burkitt's						
Status at transplant	2.48	1.62–3.78	<0.001	1.76	1.02–3.02	<0.05
Age at transplant	—	—		0.57	0.37 –0.88	<0.02
Hodgkins						
Status at transplant	—	—	—	2.31	1.16–4.62	<0.02
Lymph nodes involved at transplant	2.29	1.17–4.49	<0.02	2.33	1.07–5.10	<0.04
Mass at transplant	1.50	1.13–1.99	<0.005	—	—	—

grade NHL 8.8 months; high-grade NHL 7.1 months; lymphoblastic lymphoma 7.6 months, Burkitt's lymphoma 2.5 months; and Hodgkin's disease 4.7 months. The actuarial PFS at 4 years was as follows: low-grade NHL 42.7%; intermediate-grade NHL 34.6%; high-grade NHL 39.3%; lymphoblastic lymphoma 37.7%; Burkitt's lymphoma 34.9%; and Hodgkin's disease 15.5%.

Procedure-related mortality

The actuarial procedure-related mortality at 4 years was: low-grade NHL 38.0%;. intermediate-grade NHL 41.8%; high-grade NHL 33.0%; lymphoblastic lymphoma 33.2%; Burkitt's lymphoma 30.9%; and Hodgkin's disease 51.7%.

Comparison of the autologous and allogeneic populations

We compared the distribution of patient characteristics at diagnosis and transplantation in both populations. These populations were significantly different in various aspects (Table 4). Patients subjected to allogeneic transplantation tended to have a more advanced stage at diagnosis and had received more treatment before transplantation; they were younger and tended to have more blood and marrow involvement. The situation at the time of transplantation indicated that they tended to be transplanted with a worse disease status (Table 5) and received TBI more often. The source of stem cells also differed, with allogeneic transplants receiving mainly BM (82.5%) rather than peripheral blood stem cells (16.8%): 53.8% of autologous transplants were carried out using peripheral blood progenitor cells.

The relative proportion of allogeneic/autologous procedures according to histological subtype is shown in Table 4. A total of 7.5% of patients reported to the EBMT undergoing transplantation procedures who could be assigned to these histological subgroups received allogeneic transplantation, with the rest undergoing autologous procedures. Only 3.3% of patients with Hodgkin's disease received allogeneic transplantation as the first transplantation procedure.

Cox regression analysis was performed on patient characteristics both at diagnosis and transplantation to determine significant prognostic factors, and in particular to examine the influence of allogeneic as opposed to autologous transplantation on outcome. This analysis was initially restricted to patients for whom complete data of possible prognostic factors had been reported to the Registry. Some of these factors were shown not to affect outcome and were dropped from the analysis. Overall, the factors that were found to have significant effects on OS PFS or relapse rate were as follows: bone marrow involvement at diagnosis, age at diagnosis, age at transplant, status at transplant, largest mass at transplant, number of first line treatments, and year of transplant. The degree or significance of their effects differed with the different histological subtypes of lymphoma. Autologous *vs* allogeneic transplant type also had a significant effect on the three outcome measurements, but there were interactions with year of transplant. These complications led to the decision to use the matched analysis method to examine outcome differences between allogeneic and autologous transplantation.

Matched analysis

With the information obtained through multivariate analysis, we selected the variables used to match the allogeneic to the autologous population. Matching was

Table 4 All patients. characteristics at diagnosis

	Autologous		*Allogeneic*		*P-value*
Number of patients	14687		1185		
Age at diagnosis					
Median	35.5		29.2		<0.001
Range	0.3–83.8		1.9–73.6		
	Numbers	*%*	*Numbers*	*%*	
Gender	8937	61.0	772	65.6	
Male	5708	39.0	405	34.4	0.001
Female	42		8		
Missing					
LDH at diagnosis					
Normal	2099	78.3	302	74.9	
High	580	21.7	101	25.1	NS
Missing	12008		782		
Mass at diagnosis					
<5 cm	1935	31.1	130	24.9	
5–10 cm	1791	28.7	114	21.8	
>10 cm	1484	23.8	80	15.3	<0.001
Mass not measurable	1025	16.4	199	38.0	
Missing	8452		662		
Involvement					
BM/blood/CNS involvement	2168	28.6	321	52.2	<0.001
No above involvement	5414	71.4	351	47.8	
Missing	7105		513		
Number of lines of treatment					
1 or 2	1223	44.7	83	34.9	
3 or more	1515	55.3	155	65.1	0.003
Missing	11949		947		
Splenectomy					
No	3551	88.5	191	91.4	
Yes	463	11.5	18	8.6	NS
Missing	10673		976		
Lymphoma type					
Low-grade NHL	2047	13.9	231	19.5	
Intermediate-grade NHL	2863	19.5	147	12.4	
High-grade NHL	3232	22.0	255	21.5	
Lymphoblastic	1332	9.1	314	26.5	
Burkitt's	416	2.8	71	6.0	
Hodgkin's	4797	32.7	167	14.1	<0.001
Stage					
I	540	5.9	29	3.9	
II	2159	23.4	100	13.3	
III	2139	23.2	116	15.4	
IV	4370	47.5	507	67.4	<0.001
Missing	5479		433		
B-symptoms					
Yes	3008	36.4	200	28.1	<0.001
No	5250	63.6	511	71.9	
Missing	6429		474		

performed on the basis of one allogeneic patient to three autologous patients: the variables matched and degree of matching are listed in Table 6. The matching was over 90% exact for all variables for all lymphoma types, but the quality of the matching was impaired by the amount of missing data in mass at transplant and BM involvement at diagnosis when these variables were considered to be of importance.

The log-rank analysis of end points indicated that OS was always better for autologous than for allogeneic patients (Figure 1; see Table 7 for numbers at risk). PFS was the same in both the autologous and allogeneic groups

Table 5 All patients: characteristics at transplantation

	Autologous		*Allogeneic*		*P-value*
Age at transplant					
Median	37.8		31.5		<0.001
Range	1–84.2		1.9— 74.7		
	Numbers	*%*	*Numbers*	*%*	
Year of transplant					
<1988	1399	9.5	193	16.3	
1989–90	1177	8.0	145	12.2	
1991–92	1963	13.4	179	15.1	
1993	1736	11.8	107	9.0	
1994	1847	12.6	126	10.6	
1995	2220	15.1	127	10.7	
1996	2283	15.5	148	12.5	
1997–98	2062	14.1	160	13.5	<0.001
Missing	0		0		
Status at transplant					
1st CR	2988	21.4	241	22.3	
CR>1	2988	21.4	270	24.9	
Chemosensitive	5571	40.0	336	31.1	
Chemoresistant	2391	17.1	235	21.7	
At diagnosis	12	0.1	—	—	<0.001
Missing	737		103		
Mass at transplant					
No mass (in CR)	5976	60.1	511	62.5	
<5 cm	2475	24.9	154	18.8	
5–10 cm	866	8.7	40	4.9	
>10 cm	328	3.3	19	2.3	
BM/blood/CNS involvement	292	2.9	94	11.5	<0.001
Missing	4750		367		
TBI					
No	10548	80.6	313	28.6	
Yes	2540	19.4	782	71.4	<0.001
Missing	1599		90		
Cell source					
Bone marrow	5748	40.9	798	82.5	
Peripheral blood	7563	53.8	162	16.8	
Both	747	5.3	7	0.7	<0.001
Missing	629		218		

Table 6 Matching summary

Lymphoma type	*Prognostic factor*	*Degree of matching (%)*		
		Exact	*Off by no more than one level*	*% matched as missing*
Low-grade NHL	Status at transplant	97.6	99.7	8.3
	Year of transplant	87.4	96.0	0
	Age at diagnosis	93.8	97.7	1.4
	Age at transplant	83.4	96.5	0
	Mass at transplant	76.4	81.3	38.0
Intermediate-grade NHL	Status at transplant	99.2	100.0	2.5
	Year of transplant	86.9	99.4	0
	Age at transplant	94.8	99.2	0
	Mass at transplant	86.5	93.8	28.6
High-grade NHL	Status at transplant	99.5	100.0	8.6
	Year of transplant	89.1	97.5	0
	Age at transplant	88.2	99.7	0
	Mass at transplant	86.2	92.9	26.7
	BM involvement diagnosis	91.8	96.9	36.9
Lymphoblastic	Status at transplant	92.9	98.9	5.4
	Year of transplant	85.9	94.9	0
Burkitt's	Status at transplant	94.8	96.5	8.5
	Year of transplant	80.6	93.1	0
	Disease duration	95.1	98.6	0
Hodgkin's	Status at transplant	99.3	100.0	15.2
	Year of transplant	94.2	97.4	0
	Age at diagnosis	99.3	100.0	4.8
	Age at transplant	92.8	99.5	0
	Mass at transplant	83.0	87.2	46.9

for low-grade and intermediate-grade NHL, but better in the autologous group for the other types of NHL and for Hodgkin's. The relapse rate was better in the allogeneic groups for low-, intermediate- and high-grade NHL and for lymphoblastic lymphoma, it was equivalent for Burkitt's lymphoma, and worse in the allogeneic group for Hodgkin's disease (Figure 1a–e; Table 7). Treatment-related mortality was always worse in the allogeneic groups (Figure 2a and b; Table 7).

Discussion

We report the results of 1185 allogeneic hematopoietic stem cell transplants for lymphoma reported to the EBMT Registry between 1982 and 1998. Although allogeneic transplantation is occasionally performed to treat relapse after prior autologous procedures,[13–15] this study restricted the analysis to allografts carried out as the first transplantation procedure.

We divided the patients into six subgroups according to the histology based upon the Working Formulation.[11] A reclassification, according to the REAL system, was not possible since most of the procedures in these two groups were performed prior to its introduction.[12] The results were compared with the 14 687 autologous procedures reported to the Registry for patients for whom similar histological classification was possible. The study confirms that over the last two decades, the use of autologous transplantation has been much more widespread than allogeneic transplantation as reported to the EBMT: over the same period the number of autologous procedures exceeds the number of allografts more than 10-fold. Patients with lymphoblastic lymphoma and Burkitt's lymphoma appeared most likely to receive an allograft (20% of all transplantation procedures in these two groups were allografts) and the majority of these were performed in first or second CR. The use of allografts in low-, intermediate- and high-grade NHL was relatively uncommon. In Hodgkin's disease the use of allogeneic transplantation was even less common: only 167 allograft patients reported to the EBMT compared to 4797 autologous procedures.

The rather conservative use of these procedures seems to be justified since across all histological subtypes, the reported toxic death rate is alarmingly high, particularly for Hodgkin's disease in which the actuarial treatment-

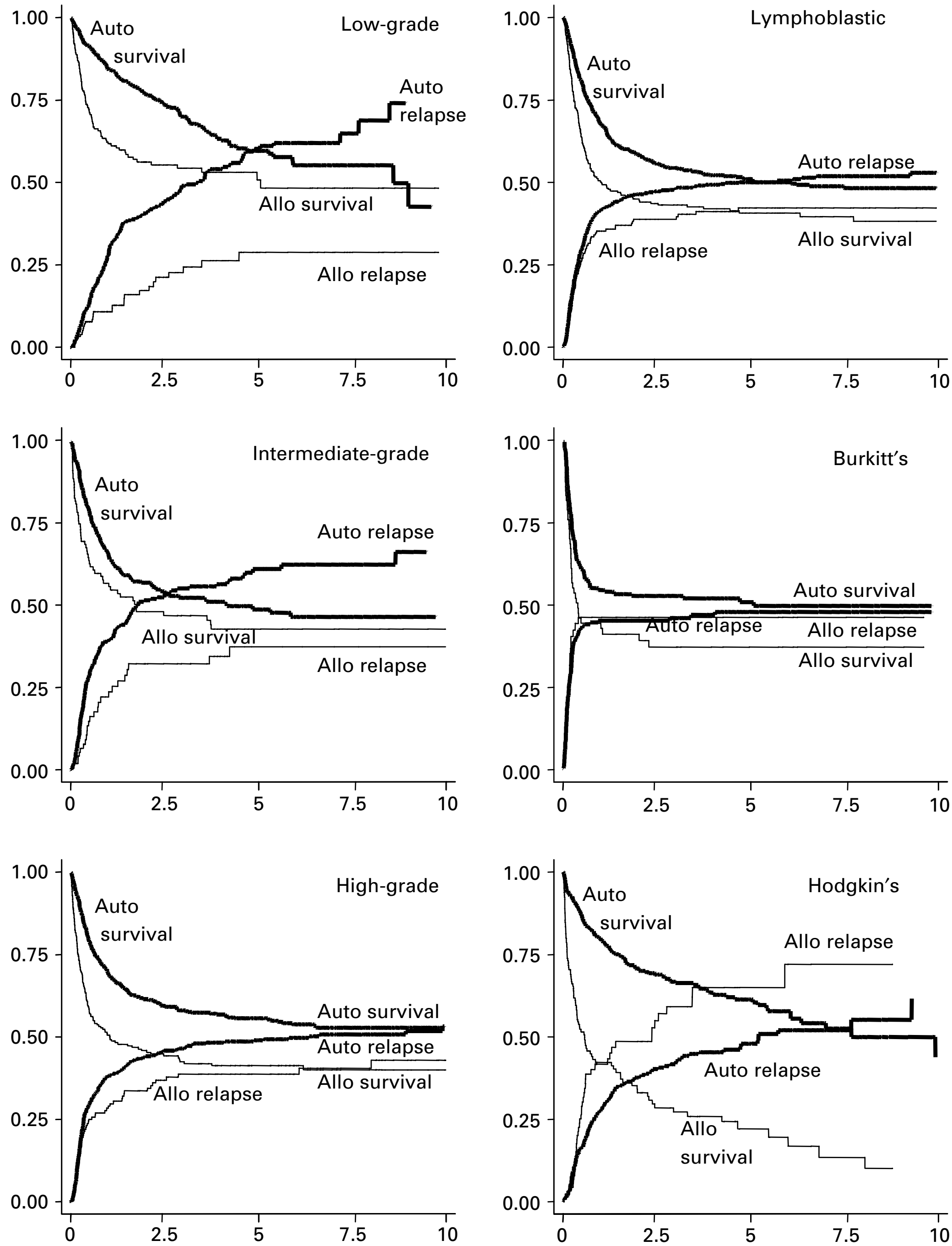

Figure 1 PRM by autologous *vs* allogeneic transplant groups.

related mortality at 4 years is 51.7%. The increased mortality rate of allogeneic procedures compared to autologous procedures is well-recognized and due in part to the additional immunosuppression associated with allografts and the role of GVHD.[9,16,17] The particularly high toxicity of Hodgkin's disease allografts may be a reflection of the disproportionately large proportion of patients with resistant disease undergoing allografts: this group of patients is known to suffer increased treatment-related mortality even when undergoing autologous transplantation,[16] and this problem may be potentiated by the allogeneic procedure.

The increased toxicity of allografting is largely responsible for the disappointing OS in these patients. We have attempted to compare these results with those of autologous transplantation using a matched-pair analysis. In all six histological subcategories, the actuarial OS obtained with autologous transplantation procedures is superior to that obtained with allogeneic transplantation.

Clearly, there is a fundamental problem in terms of treatment-related mortality that must be addressed as a priority in centers advocating allogeneic transplantation for lymphoma patients. If such a modality is to be pursued, then this is often in the hope that allogeneic procedures will

Table 7 Numbers at risk

	Lymphoma type	*Transplant*	*Interval from transplant*				
			Start	*2.5 years*	*5 years*	*7.5 years*	*10 years*
Overall survival	Low-grade	Auto	648	210	73	20	6
		Allo	216	59	22	9	1
	Intermediate-grade	Auto	360	116	50	21	8
		Allo	120	40	19	12	5
	High-grade	Auto	765	287	168	86	37
		Allo	255	80	53	27	9
	Lymphoblastic	Auto	942	340	164	86	39
		Allo	314	95	50	32	18
	Burkitt's	Auto	213	79	44	28	11
		Allo	71	19	13	8	3
	Hodgkins	Auto	435	173	75	23	8
		Allo	145	25	10	5	3
Relapse rate	Low-grade	Auto	648	148	49	12	3
		Allo	216	55	21	9	1
	Intermediate-grade	Auto	360	92	36	16	6
		Allo	120	35	18	12	5
	High-grade	Auto	765	246	148	74	32
		Allo	255	73	49	27	9
	Lymphoblastic	Auto	942	304	153	79	37
		Allo	314	89	46	30	16
	Burkitt's	Auto	213	77	42	27	10
		Allo	71	19	13	8	3
	Hodgkin's	Auto	435	131	56	17	7
		Allo	145	22	6	3	2
Procedure-related mortality	Low-grade	Auto	648	202	70	19	6
		Allo	216	59	22	9	1
	Intermediate-grade	Auto	360	116	50	21	8
		Allo	120	40	19	12	5
	High-grade	Auto	765	287	168	86	37
		Allo	255	78	53	27	9
	Lymphoblastic	Auto	942	355	162	86	39
		Allo	314	93	49	31	18
	Burkitt's	Auto	213	79	44	28	11
		Allo	71	19	13	8	3
	Hodgkin's	Auto	435	172	75	23	8
		Allo	145	24	10	5	3

produce a therapeutic graft-versus-lymphoma effect.[16,18] Allogeneic transplantation also affords the benefit of having a hematopoietic stem cell source free of tumor contamination. Both of these effects lead to a theoretically lower relapse rate in lymphoma allografts.

The presence of a lower relapse rate in lymphoma allografts compared to autografts was confirmed by this analysis. Previous analysis of the EBMT Registry detected a lower relapse rate in patients with lymphoblastic lymphoma.[10] This finding was confirmed by our analysis. Furthermore, allogeneic transplants produced a lower relapse rate than autologous procedures in patients with low-, intermediate-, and high-grade NHL. The superiority of allogeneic procedures in terms of relapse rate in patients with indolent lymphoma is particularly striking and has been reported by other groups.[19–25]

It is not possible to determine from our analysis whether the reduced relapse rate is consequent upon a graft-versus-lymphoma effect or due to the hematopoietic stem cell source being free of tumor contamination. We did, however, find some evidence that a certain degree of GvHD may be associated with a lower relapse rate in some lymphoma types. Such findings are reminiscent of well-established data on leukaemia patients where increased severity of GvHD is associated with a lower relapse rate.[26] Indeed, the presence of at least a degree of graft-versus-lymphoma effect appears likely in allogeneic transplantation and the existence of this phenomenon is supported by the reports of success with donor lymphocyte infusions for lymphoma[27] and of putative graft-versus-lymphoma effects following nonmyeloablative therapy and HLA-mismatched bone marrow transplantation.[8] However, due to the paucity of data on acute GvHD in our subset, our results are preliminary and this issue should be further explored with a larger data set. Owing to incomplete data we were unable to analyze the influence of chronic GvHD on outcome. It is possible that the potential of the graft-versus-lymphoma phenomenon may be best utilized using non-myeloablative chemotherapy followed by allogeneic stem cell transplantation. Preliminary reports have demonstrated the successful use of such protocols in lymphoma.[28–31] Such protocols may be expected to decrease the currently high toxicity of allogeneic procedures, as may the increased use of allogeneic peripheral blood stem cells.[32,33] It remains to be seen whether low-intensity allograft protocols may be of therapeutic benefit in the challenging

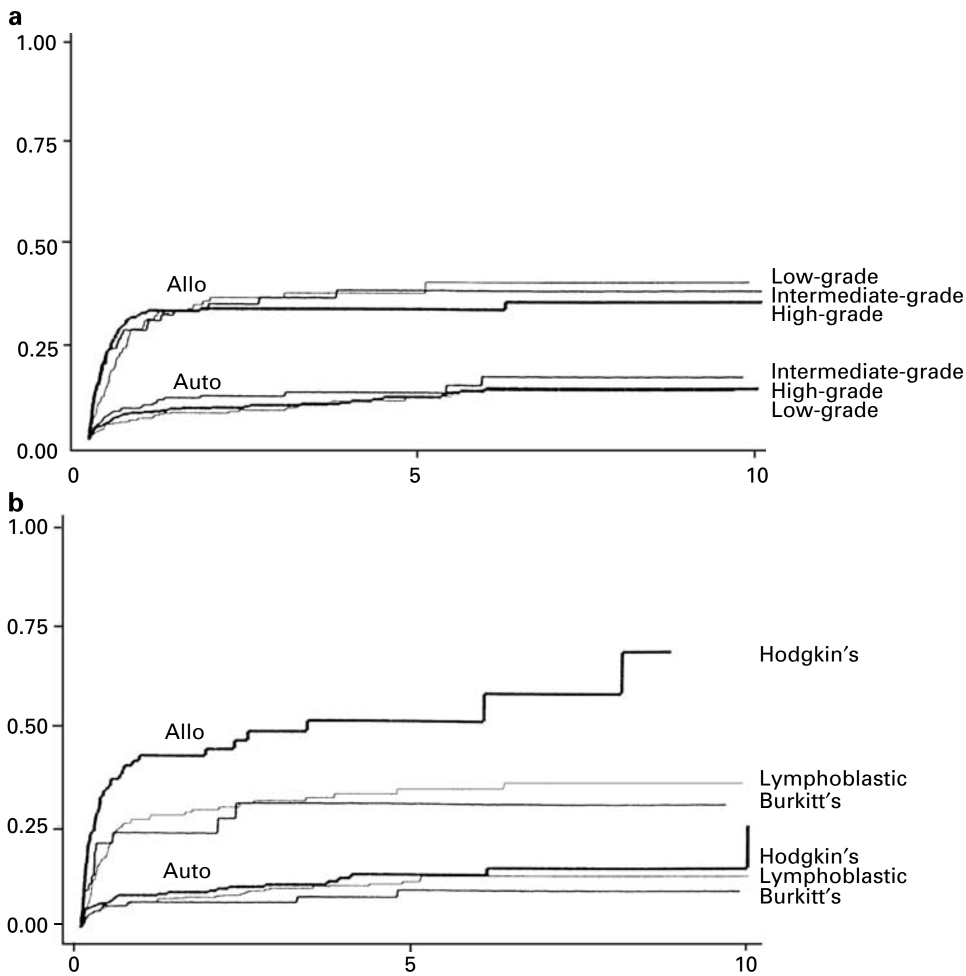

Figure 2 PRM by autologous *vs* allogeneic transplant groups: (a) low-, intermediate- and high-grade; (b) Hodgkin's lymphoblastic and Burkitt's.

setting of chemoresistant lymphoma: preliminary data suggest that the outcome of such procedures is rather poor in this cohort of patients.[28]

In conclusion, the EBMT experience supports the beneficial effects of allogeneic procedures in producing a lower relapse rate than autologous transplantation in lymphoma patients. There has been, however, a disappointingly high treatment-related mortality associated with these procedures, which in this analysis more than outweighs the benefits of a lower relapse rate. Whether recent improvements in the supportive care of patients undergoing high-dose therapy will translate to a reduction in the toxic death rate great enough to permit beneficial use of allogeneic procedures remains to be seen. In the meantime, the precise role of allogeneic transplantation in lymphoma has still to be defined and autologous transplantation remains the current benchmark therapy for patients requiring high-dose therapy.

Acknowledgements

We gratefully acknowledge the collaboration of the large number of contributing transplant centers throughout and outside Europe. The following centers have registered over 50 lymphoma transplants with the EBMT, which have been used in this study:

Australia: Alfred Hospital, Melbourne; Royal Perth Hospital, Perth. *Austria*: AKH, Wein. *Belgium*: University Hospital, Leuven; Institut Jules Bordet, Brussels; Cliniques Universitaires St. Luc, Brussels; A.Z. Sint-Jan, Brugge; University of Liege, Liege. *Croatia*: University Hospital Centre-Rebro, Zagreb. *Czech Republic*: Charles University Hospital, Pilsen; Charles University Hospital, Praha. *Denmark*: Rigshospitalet, Copenhagen; Herlev Hospital, Herlev. *Finland*: Central Hospital, Turku; University Central Hospital, Helsinki. *France*: Hôpital Necker, Paris; Hôpital E. Herriot, Lyon Cedex 08; Hôpital Saint Antoine, Paris; Hotel Dieu, Paris; Institut Paoli Calmettes, Marseille; Hôpital St Jacques, Besançon; Centre Leon Berard, Lyon; Hôpital Nord, Saint Etienne; Centre Hospitalier Intercommunal, Creteil; Hotel Dieu, Nantes; Pitie-Salpetriere, Paris; Hôpital La Miletrie, Poitiers; Hôpital du Haut Leveque, Pessac; Hôpital A. Michallon, Grenoble; Hôpital Bretonneau, Tours; Centre Jaen Perrin, Clermont Ferrand; Hôpital Claude Huriez, Lille; Institut Gustave Roussy, Villejuif; Hôpital de Purpan, Toulouse; CHRU, Angers; Hôpital Percy, Clamart; Institut Gustave Roussy, Villejuif; Hôpital St. Louis, Paris. *Germany*: Universität Ulm, Ulm; Christian-Albrechts-University, Kiel; University Hospital, Essen; Medical School, Hannover; Universität Frankfurt, Frankfurt; Klinikum Nürnberg, Nürnberg;

University of Saarland, Homburg/Saarland. *Greece*: The George Papanicolaou, Exokhi; Evangelismos Hospital, Athens. *Italy*: Ospedale San Martino, Genova; Centro Trapianti di Midollo Osseo, Cremona; Azienda Ospedaliera S. Giovanni, Torino; La Sapienza, Rome; Hospital San Orsola, Bologna; Centro Trapianti Midollo Osseo, Parma; IRCCS, Milano; Policlinico San Matteo, Pavia; Ospedale S. Camillo, Rome; Hospital San Maurizio, Bolzano; Ospedale di Careggi, Firenze; Ospedale Civile, Ravenna; Ospedale V. Cervello, Palermo; Hospital Casa Sollievo, San Giovanni Rotondo; Universita di Modena, Modena; Istituto Nazionale Tumori, Milano; Universita di Verona, Verona; Universita'degli Studi di Bari, Bari; Ospedale Bergamo, Bergamo; Universita di Udine, Udine; Universita Tor Vergata, Rome; Ospedale di Torrette, Ancona; Ospedale Oncologico, Cagliari. *Netherlands*: University Hospital, Utrecht; Daniel den Hoed Cancer Centre, Rotterdam; University Hospital St Radboud, Nijmegen; University Hospital Maastricht, Maastricth. *Norway*: The Norwegian Radium Hospital, Oslo. *Portugal*: Centro Porto, Porto. *Spain*: Hospital Clinic, Barcelona; Hospital de la Princesa, Madrid; Marqués de Valdecilla, Santander; Hospital Santa Creu i Sant Pau, Barcelona; Hospital Universitario 'La Fé', Valencia; Hospital Clinico, Salamanca; Hospital Duran i Reynals, Barcelona; Hospital Universitario 'Virgen delR, Sevilla. *Sweden*: Huddinge University, Huddinge; University Hospital, Uppsala; University Hospital, Lund; Sahlgrenska University, Goeteborg. *Switzerland*: University Hospital, Zurich. *United Kingdom*: Royal Free Hospital, London; Royal Marsden Hospital, Sutton; University College London Hospital, London; Western General Hospital, Edinburgh; Glasgow Royal Infirmary, Glasgow; Newcastle General Hospital, Newcastle upon Tyne; Heartlands Hospital, Birmingham; Department of Haematology, Liverpool; Addenbrookes Hospital, Cambridge; University of Southampton, Southampton; City Hospital, Nottingham; Guy's Hospital, London; City Hospital, Belfast; St Bartholomews Hospital, London; Christie NHS Trust Hospital, Manchester.

References

1 Chopra R, McMillan AK, Linch DC *et al*. The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients. *Blood* 1993; **81**: 1137–1145.
2 Linch DC, Winfield D, Goldstone AH *et al*. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341**: 1051–1054.
3 Mills W, Chopra R, McMillan A *et al*. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 1993; **13**: 588–595.
4 Philip T, Armitage JO, Spitzer G *et al*. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1987; **316**: 1493–1498.
5 Philip T, Guglielmi C, Hagenbeek A *et al*. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma [see comments]. *N Engl J Med* 1995; **333**: 1540–1545.
6 Leonard BM, Hetu F, Busque L *et al*. Lymphoma cell burden in progenitor cell grafts measured by competitive polymerase chain reaction: less than one log difference between bone marrow and peripheral blood sources. *Blood* 1998; **91**: 331–339.
7 Verdonck LF. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma: updated results of the Utrecht experience. *Leuk Lymphoma* 1999; **34**: 129–136.
8 Sykes M, Preffer F, McAfee S *et al*. Mixed lymphohaemopoietic chimerism and graft-versus-lymphoma effects after non-myeloablative therapy and HLA-mismatched bone-marrow transplantation. *Lancet* 1999; **353**: 1755–1759.
9 Milpied N, Fielding AK, Pearce RM *et al*. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. European Group for Blood and Bone Marrow Transplantation. *J Clin Oncol* 1996; **14**: 1291–1296.
10 Chopra R, Goldstone AH, Pearce R *et al*. Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group Registry data. *J Clin Oncol* 1992; **10**: 1690–1695.
11 National Cancer Institute. Sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of Working Formulation for clinical usage. *Cancer* 1982; **29**: 2112–2129.
12 Harris NL, Jaffe ES, Stein H *et al*. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84**: 1361–1392.
13 de Lima M, van Besien K, Giralt SA *et al*. Bone marrow transplantation after failure of autologous transplant for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 1997; **19**: 121–127.
14 Moreau P, Mechinaud F, Mahe B *et al*. Successful allogeneic bone marrow transplantation for early relapse after autologous bone marrow transplantation in two cases of aggressive high-grade non-Hodgkin's lymphoma. *Bone Marrow Transplant* 1996; **18**: 665–667.
15 Tsai T, Goodman S, Saez R *et al*. Allogeneic bone marrow transplantation in patients who relapse after autologous transplantation. *Bone Marrow Transplant* 1997; **20**: 859–863.
16 Jones RJ, Ambinder RF, Piantadosi S *et al*. Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation. *Blood* 1991; **7**: 649–653.
17 Dann EJ, Daugherty CK, Larson RA. Allogeneic bone marrow transplantation for relapsed and refractory Hodgkin's disease and non-Hodgkin's lymphoma. *Bone Marrow Transplant* 1997; **20**: 369–374.
18 Ratanatharathorn V, Uberti J, Karanes C *et al*. Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma. *Blood* 1994; **84**: 1050–1055.
19 Copelan EA, Kapoor N, Gibbins B *et al*. Allogeneic marrow transplantation in non-Hodgkin's lymphoma. *Bone Marrow Transplant* 1990; **5**: 47–50.
20 Schouten IC, Raemaekers JJ, Kluin NH *et al*. High-dose therapy followed by bone marrow transplantation for relapsed follicular non-Hodgkin's lymphoma. Dutch HOVON Group. *Ann Hematol* 1996; **73**: 273–277.
21 van Besien KW, Khouri IF, Giralt SA *et al*. Allogeneic bone marrow transplantation for refractory and recurrent lowgrade lymphoma: the case for aggressive management. *J Clin Oncol* 1995; **13**: 1096–1102.
22 van Besien KW, Mehra RC, Giralt SA *et al*. Allogeneic bone marrow transplantation for poor-prognosis lymphoma: response, toxicity and survival depend on disease histology. *Am J Med* 1996; **100**: 299–307.

23 van Besien KW, Sobocinski KA, Rowlings PA *et al*. Allogeneic bone marrow transplantation for low-grade lymphoma. *Blood* 1998; **92**: 1832–1836.
24 Attal M, Socie G, Molina L *et al*. Allogeneic bone marrow transplantation for refractory and recurrent follicular lymphoma: a case-matched analysis with autologous transplantation from the French bone marrow transplant group registry data. *Blood* 1997; **20**: 1120a.
25 Mandigers CM, Raemaekers JM, Schattenberg AV *et al*. Allogeneic bone marrow transplantation with *T*-cell-depleted marrow grafts for patients with poor-risk relapsed low-grade non-Hodgkin's lymphoma. *Br J Haematol* 1998; **100**: 198–206.
26 Sullivan KM, Weiden PL, Storb R *et al*. Influence of acute and chronic graft-versus-host disease on relapse and survival after bone marrow transplantation from HLA-identical siblings as treatment of acute and chronic leukemia. *Blood* 1989; **73**: 1720–1728.
27 van Besien KW, de Lima M, Giralt SA *et al*. Management of lymphoma recurrence after allogeneic transplantation: the relevance of graft-versus-lymphoma effect. *Bone Marrow Transplant* 1997; **19**: 977–982.
28 Khouri IF, Keating M, Champlin R *et al*. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol* 1998; **16**: 2817–2824.
29 Kottaridis PD, Chakraverty R, Milligan D *et al*. A non-myeloablative regimen for allografting high-risk patients: low toxicity, stable engraftment without GVHD, disease control and potential for GVL with adoptive immunotherapy. *Blood*. 1999; **94** (Suppl 1): 348a.
30 Khouri I, Lee M-S, Palmer L *et al*. Transplant-lite using fludarabine-cyclophosphamide (FC) and allogeneic stem cell transplant (AlloSCT) for low-grade lymphoma (LGL). *Blood*. 1999; **94** (Suppl 1): 348a.
31 Russell NH, Cull G, Byrne JL *et al*. Evaluation of non-myeloablative conditioning combining BEAM with in vivo pre-transplant Campath-IG for allogeneic transplantation in patients with lymphoma. *Blood* 1999; **94** (Suppl. 1): 348a.
32 Korbling M, Przepiorka D, Huh YO *et al*. Allogeneic blood stem cell transplantation for refractory leukemia and lymphoma: potential advantage of blood over marrow allografts. *Blood* 1995; **85**: 1659–1665.
33 Bensinger W, Martin P, Clift R *et al*. A prospective randomised trial of peripheral blood stem cells or marrow for patients undergoing allogeneic transplantation for hematologic malignancies. *Blood* 1999; **94** (Suppl. 1): 368a.