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ORIGINAL REPORT

Reduced-Intensity Conditioning Compared With Conventional Allogeneic Stem-Cell Transplantation in Relapsed or Refractory Hodgkin's Lymphoma: An Analysis From the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

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ABSTRACT

Purpose
To compare the clinical outcome in terms of nonrelapse mortality (NRM), relapse rate (RR), overall survival (OS), and progression-free survival (PFS) in patients with relapsed Hodgkin's lymphoma (HL) treated with reduced-intensity conditioning (RIC) or myeloablative conditioning followed by allogeneic stem-cell transplantation (alloSCT).

Patients and Methods
A total of 168 patients with HL undergoing a first alloSCT (RIC, n = 89; myeloablative conditioning, n = 79) between January 1997 and December 2001 and registered in the European Group for Blood and Marrow Transplantation database were analyzed.

Results
NRM was significantly decreased in the RIC group (hazard ratio [HR], 2.85; 95% CI, 1.62 to 5.02; $P < .001$). OS was better in the RIC group (HR, 2.05; 95% CI, 1.27 to 3.29; $P = .04$) and there was a trend for better PFS in the RIC group (HR, 1.53; 95% CI, 0.97 to 2.40; $P = .07$). RR was higher in the RIC group in univariate but not in multivariate analysis. The development of chronic graft-versus-host disease (GVHD) significantly decreased the incidence of relapse, which translated into a trend for a better PFS.

Conclusion
The lower incidence of NRM in the RIC group is encouraging, particularly because these patients experienced adverse pretransplantation characteristics more frequently. This analysis also indicates the existence of a graft-versus-HL effect correlated to the development of GVHD. Additional efforts to reduce the high RR seen in both groups of patients will be necessary to improve the modest PFS (31% *v* 27%) and OS (59% *v* 36%) for patients prepared with RIC or myeloablative conditioning.

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INTRODUCTION

Autologous stem-cell transplantation (ASCT) is considered to be the standard of care for patients with relapsed or refractory Hodgkin's lymphoma (HL), leading to durable responses in 50% to 60% of the patients with chemotherapy-sensitive relapse and in 25% to 40% of refractory patients.[1-3] Those patients who experience relapse after ASCT as well as those truly refractory to first-line therapy are considered candidates for more experimental approaches such as allogeneic stem-cell transplantation (alloSCT).

Interest in the use of alloSCT derives not only from the cytoreduction caused by chemoradiotherapy, but also from the potential benefit of an immune-mediated graft-versus-tumor effect.[4] The role of alloSCT in patients with relapsed or refractory HL has been highly controversial. Although several series suggested that alloSCT may be associated with a clinically significant graft-versus-HL effect and a lower relapse rate compared with ASCT,[5-8] retrospective analyses from the Center for International Bone Marrow Transplant Registry (CIBMTR)[9] and the European Group for Blood and Marrow Transplantation (EBMT),[10] reported disappointing results with alloSCT in HL mainly due to an extremely high nonrelapse mortality (NRM).

Reduced-intensity conditioning (RIC) followed by alloSCT (alloRIC) currently is being evaluated in patients who are considered poor candidates for conventional alloSCT.[11-13] RIC could be of particular benefit for HL patients undergoing alloSCT by reducing the high NRM. Several groups reported encouraging results with alloRIC in HL.[14-19] The 100-day NRM decreased to less than 15% in patients who received unmanipulated grafts[14,17,19] and progression-free survival (PFS) increased to 30% to 50%; however, follow-up was short (1.5 to 2 years).

A direct comparison between conventional and RIC protocols for HL has not been performed. Therefore, the Lymphoma Working Party of the EBMT sought to determine the outcomes of patients with refractory or relapsed HL undergoing alloSCT after either a myeloablative or an RIC protocol.

PATIENTS AND METHODS

Patients, Transplantation Characteristics, and Definitions

The EBMT is a voluntary organization comprising 548 transplantation centers. Ninety-eight alloSCT centers participated in this retrospective study. Participants are required once a year to report all consecutive transplantations and follow-up. The Lymphoma Working Party validates and checks submitted data to ensure data quality. All centers completed an extensive case report form per eligible patient. Data for individual patients were derived from both the EBMT database and from questionnaires distributed to each center. Follow-up questionnaires were sent to obtain missing data. The local ethics committees approved the different trials onto which the patients were included and all patients gave written informed consent to participate in the trials.

Included in the study were 168 patients with HL. Only patients who underwent a first alloSCT from a matched unrelated donor (MUD) or an HLA-identical sibling between January 1997 and December 2001 were included (Table 1). Truly myeloablative conditioning regimens included combinations of cyclophosphamide with high-dose total-body irradiation (TBI; $\geq$ 8 Gy) or high-dose busulfan (16 mg/kg total dose by mouth or equivalent dose intravenously [IV]), with or without other cytotoxic agents. The rest of the conditioning regimens were included under the RIC definition: carmustine 300 mg/m^2 IV, etoposide 600 to 800 mg/m^2 IV, cytarabine 800 to 1,600 mg/m^2 IV, melphalan 100 to 140 mg/m^2 IV (BEAM regimen), and fludarabine plus intermediate doses of one or two alkylating agents or low-dose TBI (2 to 4 Gy). Intermediate doses of alkylating agents consisted of busulfan 8 to 10 mg/kg orally, melphalan 80 to 140 mg/m^2, cyclophosphamide 60 to 120 mg/kg, or thiotepa (5 to 10 mg/kg. BEAM was included in the RIC group taking into account the results in terms of low NRM and good clinical outcome presented by Faulkner et al.[20]

Although antithymocyte globulin or alemtuzumab was used for T-cell depletion before RIC or conventional allografting in comparable percentages of patients, other graft-versus-host disease (GVHD) prophylaxis differed between both groups. In vitro T-cell depletion was more frequent in the conventional group (15.7% *v* 1.2%; $P = .001$), as was the combination of cyclosporine and methotrexate in those patients from the conventional group without in vitro T-cell depletion (73.8% *v* 60.0%).

Patients in the myeloablative group were allografted earlier than those in the RIC group: 41.8% received their graft in 1997 to 1998, whereas only 15.7% of the RIC group was allografted during this period (Table 1). More patients prepared with myeloablative regimens have undergone transplantation with bone marrow, whereas the RIC patients frequently received peripheral blood. RIC patients had been more heavily pretreated: time interval between diagnosis and alloSCT was longer (mean, 42 months; range, 4 to 242 months *v* mean, 31 months; range, 7 to 181 months; $P = .007$) and more patients had experienced treatment failure after a prior ASCT (61.8% *v* 40.5%; $P = .005$). Of the 81 patients undergoing an alloSCT without a prior ASCT, 30% had bone marrow involvement at alloSCT, 75% had experienced treatment failure after $\geq$ three lines of therapy before transplantation, and 20% had primary refractory disease at alloSCT.

Histologic diagnosis was based on local review and patients were staged according to the Ann Arbor system.[21] Disease status at transplantation was classified as chemosensitive disease including all patients who had shown at least a partial remission, chemoresistant disease including patients with primary refractory disease or refractory relapse, or untreated relapse. Patients who survived more than 90 days after alloSCT without evidence of tumor were classified as having experienced complete remission. Partial remission was defined as a $\geq$ 50% reduction of all pretransplantation measurable disease for at least 1 month. Patients achieving less than 50% tumor reduction were considered nonresponders.

End Point Definitions

End points were assessed on the date of last patient contact; the database was closed in December 2006. Analysis focused on hematologic recovery, acute GVHD (aGVHD) and chronic GVHD (cGVHD), NRM, disease relapse or progression, PFS, and overall survival (OS). aGVHD and cGVHD were defined in accordance with accepted criteria.[22] Analysis of cGVHD included only patients who had achieved neutrophil recovery and survived without disease progression for more than 90 days from transplantation. Spontaneous cGVHD was defined as cGVHD appearing after the allogeneic procedure before donor lymphocyte infusions were performed.

Statistical Analysis

Probabilities of PFS and OS were estimated from the time of transplantation using Kaplan-Meier estimates. Groups were compared using the two-tailed log-rank test. The occurrence of acute and cGVHD, NRM, and disease relapse or progression was calculated using cumulative incidence estimates, taking into account the competing risk structure.[23,24] Univariate analyses of these latter outcomes were performed using univariate Cox regression models.

For multivariate analyses, the main covariates were first entered into the model; then covariates found not to be significant at the .10 level were removed from the Cox proportional hazards model in a stepwise backward manner. The proportionality assumption was checked in each situation by introducing time as a (time dependent) covariate and testing for a significant interaction with the risk factors under study. If a deviation from the proportionality assumption was found, a stratified Cox model was used. After the selection of the final models, we verified that variables previously excluded from the model did not add a significant contribution to the model. Results are presented as relative risks of failure (adverse prognostic factors *v* good prognostic factors), with the 95% CI and the *P* value. Grades 2 to 4 of aGVHD were introduced in the final models for NRM, relapse, PFS, and OS as a time-dependent covariate. To investigate the influence of cGVHD on the outcome, a landmark analysis approach was used. Multivariate analyses restricted to patients in the conventional group and in the RIC group were performed to investigate the impact of TBI in the outcome.

SPSS version 13.0 (SPSS Inc, Chicago, IL) was used for all statistical analyses with the exception of the cumulative incidence analyses, which were carried out with NCSS97 (Number Cruncher Statistical System, Kaysville, UT).

RESULTS

Hematologic Recovery After Transplantation

Median time to reach an absolute neutrophil count more than 0.5×10^9/L was calculated as 14 days in the standard group and in the RIC group (not significant). The median time to achieve a platelet count more than 20×10^9/L was 19 days in the standard group and 12.5 days in the RIC group ($P = .007$; Table 2)

GVHD

Acute GVHD developed in 39 of 73 patients (53.4%) in the myeloablative group and in 45 of 81 patients (44.4%) of the RIC group, resulting in 100-day cumulative incidences of 53% (95% CI,

Table 1. Patient Characteristics

Characteristic	Standard Myeloablative Conditioning		Reduced-Intensity Conditioning		*P*
	No. of Patients	%	No. of Patients	%	
Total No. of patients	79	47	89	53	
Period of transplantation					
1997-1998	33	41.8	14	15.7	
1999-2001	46	58.2	75	84.3	< .001
Male sex	38	48.1	45	50.6	.8
Age at diagnosis, years					.8
Median	27		26		
Range	11-60		5-61		
Age at alloSCT, years					.4
Median	31		30		
Range	12-61		9-64		
≤ 16	4	5.1	5	5.6	
≤ 35	58	73.4	63	70.8	
≥ 45	6	7.6	7	7.9	
Disease stage at diagnosis					
I-II	16	44.4	17	32.7	
III-IV	20	55.6	35	67.3	.3
Bulky disease at diagnosis	7	28.0	10	22.2	.8
No. of lines of therapy before alloSCT					
1-2	22	27.8	14	15.7	
≥ 3	57	72.2	75	84.3	.06
Previous ASCT	32	40.5	55	61.8	.005
Time from diagnosis to alloSCT, months					.007
Median	31		42		
Range	7-181		4-242		
Donor sex					
Patient male, donor female	16	21.6	21	25.0	.7
CMV risk group					
Patient positive, donor positive or negative (high risk)	28	49.1	49	60.5	
Patient negative, donor positive or negative (intermediate to low risk)	10	17.6	8	9.9	
Patient negative, donor negative (low risk)	19	33.3	24	29.6	.3
Donor type					
HLA-matched sibling donor	70	88.6	77	86.5	
HLA-matched URD	9	11.4	12	13.5	.8
Stem-cell source for alloSCT					
BM	33	41.8	15	16.9	
PB	46	28.2	74	83.1	.001
Disease status at alloSCT					
Chemotherapy-sensitive disease	36	45.6	40	44.9	
Chemotherapy-refractory disease	43	54.4	49	55.1	.99
Follow-up of survivors, months					
Median	76		73		
Range	12-120		17-98		.2

Abbreviations: alloSCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; CMV, cytomegalovirus; URD, unrelated donor; PB, peripheral blood; BM, bone marrow.

43% to 66%) and 44% (95% CI, 35% to 57%), respectively ($P = .05$; Table 2). There were 120 patients at risk of cGVHD. Spontaneous cGVHD developed in 20 to 52 patients (38.4%) in the myeloablative group (12 limited, five extensive, and three with unknown extent) and in 27 to 68 (39.7%) patients in the RIC group (12 limited, 13 extensive, and two with unknown extent). The 1-year cumulative incidences of cGVHD where 33% (95% CI, 22% to 48%) and 38% (95% CI, 28% to 52%), respectively ($P = .5$).

NRM

Outcomes after transplantation are listed in Table 2. Sixty patients (36% of the whole series; 39 patients in the myeloablative group and 21 patients in the RIC group) died as a result of transplantation-related causes. The 3-month and 1-year incidences of NRM were 28% and 46% in the standard group and 15% and 23% in the RIC group, respectively ($P = .001$; Table 2; Fig 1). The use of a conventional conditioning regimen (RR = 2.85; 95% CI 1.62-5.02; $P < .001$),

Table 2. Engraftment and Transplantation Outcomes per Conditioning Regimen

Outcome	Standard Myeloablative Conditioning				Reduced-Intensity Conditioning				*P*
	No. of Patients Evaluated	No.	%	95% CI	No. of Patients Evaluated	No.	%	95% CI	
Hematologic reconstitution and engraftment									
Engraftment	79	69	87.3		89	84	94.4		
Not applicable (early death)		8	10.1			4	4.5		
Primary graft failure		1	1.3			1	1.1		
Secondary graft failure		1	1.3			—			.4
Hematologic recovery									
Days to $> 0.5 \times 10^9$/L neutrophils	68				68				.3
Median		14				14			
Range		8-27				1-27			
Days to $> 20 \times 10^9$/L platelets	33				50				.007
Median		19				12.5			
Range		7-39				1-70			
Days to $> 50 \times 10^9$/L platelets	42				50				.02
Median		20				15			
Range		10-131				1-84			
GVHD									
Acute GVHD	73				81				
No acute GVHD		34	46.6			45	55.6		
Acute GVHD, any grade		39	53.4			36	44.4		.3
Grade I		14	19.2			11	13.6		
Grade II		16	21.9			17	21.0		
Grade III		6	8.2			5	6.2		
Grade IV		3	4.1			3	3.7		.8
Day of onset of aGVHD									.2
Median		17.5				22			
Range		10-90				10-85			
100-day cumulative index of aGVHD		0.53		0.43 to 0.66		0.44		0.35 to 0.57	.05
Chronic GVHD	79				89				
Patients at risk of spontaneous cGVHD (n = 120)		52	65.8			68	76.4		.09
No		32	61.5			41	60.3		
Limited		12	23.1			12	17.6		
Extensive		5	9.6			13	19.1		
Unknown extension		3	5.8			2	2.9		.4
1-year cumulative incidence of cGVHD		0.33		0.22 to 0.48		0.38		0.28 to 0.52	.5
NRM (probability)	79				89				
3 months		.28		.20 to .39		.15		.9 to .24	
1 year		.46		.37 to .58		.23		.15 to .34	
3 years		.48		.39 to .60		.24		.16 to .35	.003
Disease progression, years (probability)	79				89				
1		.27		.19 to .38		.46		.36 to .58	
3		.30		.22 to .42		.57		.47 to .68	
5		.32		.23 to .43		.58		.48 to .70	.04
Progression-free survival, years (probability)	79				89				
1		.27		.18 to .37		.31		.21 to .41	
3		.21		.13 to .30		.19		.11 to .28	.6
5		.20		.11 to .28		.18		.10 to .26	
Overall survival, years (probability)	79				89				
1		.36		.26 to .46		.59		.48 to .69	.06
3		.24		.16 to .34		.35		.24 to .45	
5		.22		.13 to .31		.28		.18 to .38	

Abbreviations: GVHD, graft-versus-host disease; aGVDH, acute GVHD; cGVHD, chronic GVHD; NRM, nonrelapse mortality.

chemorefractory disease (RR = 1.64; 95% CI 1.00-2.70; $P = .05$) and a previously failed ASCT (RR = 1.90; 95% CI 1.12-3.24; $P = .02$), significantly increased NRM. In those patients failing a prior ASCT, the use of a myeloablative alloSCT was associated with a significantly higher NRM (RR = 3.7; 95% CI 1.92-7.35; $P < .001$).

Disease Relapse or Progression

Twenty-four patients (30.4%) in the standard group and 51 patients (57.3%) in the RIC group experienced relapsed after a median time of 6 months (range, 1 to 50 months; Table 2). Nine of these patients (12%) are alive after additional treatment and 66 patients have died.

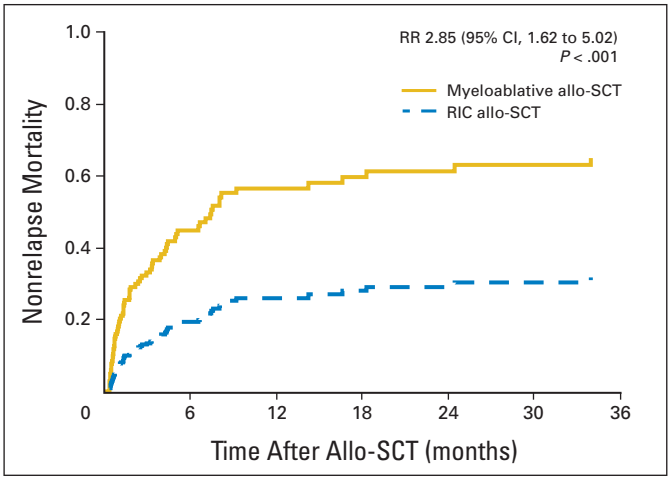

Fig 1. Nonrelapse mortality after allogeneic stem-cell transplantation (alloSCT) for Hodgkin's lymphoma according to the type of conditioning regimen, based on a Cox model. The curves represent an estimate of the probability of nonrelapse mortality adjusted by chemotherapy sensitivity of the disease at stem-cell transplantation, a previously failed autologous stem-cell transplantation, and age of the patient at alloSCT. Relative risk (RR) and *P* values are from multivariate Cox models. RIC, reduced-intensity conditioning.

Bulky disease at diagnosis was the only significant adverse prognostic factor for relapse for the whole group of patients (relative risk [RR] = 3.10; 95% CI, 1.32 to 7.24; $P = .009$). In the RIC setting, low-dose TBI was associated with a trend for higher risk of relapse (RR = 2.54; 95% CI 0.90-7.13; $P = .07$). RR was not significantly higher between conventional and RIC in the group of patients who had previously experienced treatment failure after ASCT ($P = .2$).

Survival

OS. After a median follow-up for surviving patients of 75 months (range, 12 to 120 months), 42 patients were alive (24 in the RIC group, 26.9%; 18 in the conventional group; 22.8%). Five-year OS was 22% (95% CI, 13% to 31%) for the conventional group and 28% (95% CI, 18% to 38%) for the RIC group (Table 2; Fig 2A). A previously failed ASCT (RR = 1.59; 95% CI, 1.07 to 2.35; $P = .02$), the use of myeloablative conditioning (RR = 1.62; 95% CI, 1.27 to 3.29; $P = .04$) and the presence of refractory disease (RR = 1.51; 95% CI, 1.03 to 2.21; $P = .003$) were independent adverse prognostic factors for OS. The use of low-dose TBI was associated with a lower OS in the RIC group (Table 3). The use of an RIC protocol as a salvage therapy after an ASCT was associated with a significantly better OS (RR = 2.7; 95% CI, 1.3 to 5.8; $P = .008$).

PFS. The 5-year PFS was 20% (95% CI, 11% to 28%) for the conventional group and 18% (95% CI, 10% to 26%) for the RIC group (Table 2; Fig 2B). Chemotherapy-refractory disease (RR = 1.50; 95% CI, 1.05 to 2.22; $P = .02$), bulky disease at diagnosis (RR = 2.23; 95% CI, 1.14 to 4.36; $P = .02$), and the use of a myeloablative conditioning protocol (RR = 1.53; 95% CI, 0.97 to 2.40; $P = .07$) were found to be adverse prognostic factors (Table 3). The use of low-dose TBI had a negative impact on PFS in the RIC group. In patients who experienced treatment failure after a prior ASCT, PFS was also better in the RIC group (RR = 1.6; 95% CI, 1.0 to 2.6; $P = .05$).

Impact of cGVHD on Transplantation Outcome. The impact of cGVHD on the outcome was analyzed in the whole group of patients at risk (n = 120). A landmark analysis indicated that patients developing

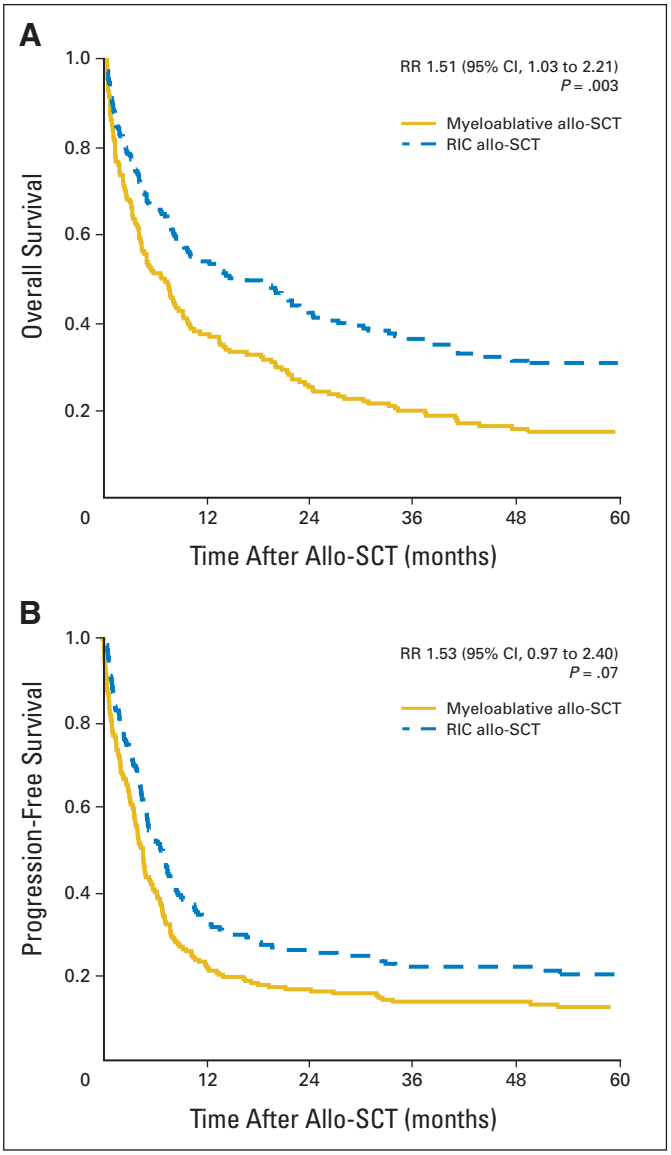

Fig 2. (A) Overall survival after allogeneic stem-cell transplantation (alloSCT) for Hodgkin's lymphoma according to the type of conditioning regimen, based on a Cox model. The curves represent an estimate of the probability of overall survival adjusted by chemotherapy sensitivity of the disease at alloSCT, a previously failed autologous stem-cell transplantation, and age of the patient at alloSCT. (B) Progression-free survival after alloSCT for Hodgkin's lymphoma according to the type of conditioning regimen, based on a Cox model. The curves represent an estimate of the probability of progression-free survival adjusted by all covariates in the model with impact in this outcome. RR, relative risk; RIC, reduced-intensity conditioning

cGVHD had a significantly decreased risk of relapse (patients with no cGVHD, RR = 1.9; 95% CI, 1.0 to 3.9; $P = .05$; Fig 3A). This effect translated into a trend for better PFS in those patients developing compared with those not developing cGVHD (RR = 1.6; 95% CI, 0.9 to 2.7; $P = .1$), with no significant impact on the NRM rate (Figs 3B and 3C).

DISCUSSION

This report represents the first comparative analysis of alloSCT after RIC or conventional myeloablative conditioning in patients with

Table 3. Prognostic Factors After Allogeneic Transplantation for HL: Multivariate Analysis

Factor	Relative Risk	95%CI	*P*
Adverse prognostic factors for nonrelapse mortality			
Myeloablative conditioning	2.85	1.62 to 5.02	<.001
Refractory disease at transplantation	1.64	1.00 to 2.70	.05
Previous failed autologous transplantation	1.90	1.12 to 3.24	.02
Age at SCT > 35 years	1.48	0.87 to 2.52	.1
Adverse prognostic factors for relapse or progression			
Reduced-intensity conditioning	2.48	0.77 to 2.79	.2
Bulky disease at diagnosis	3.10	1.32 to 7.24	.009
Refractory disease at transplant	1.51	0.95 to 2.39	.08
Multivariate analysis restricted to RIC group			
TBI-based conditioning regimen	2.54	0.90 to 7.13	.07
Adverse prognostic factors for PFS			
Myeloablative conditioning	1.53	0.97 to 2.40	.07
Refractory disease at transplantation	1.50	1.05 to 2.22	.02
Bulky disease at diagnosis	2.23	1.14 to 4.36	.02
Age at SCT > 35 years	1.34	0.91 to 1.98	.1
Multivariate analysis restricted to RIC group			
TBI-based conditioning regimen	2.3	1.06 to 5.09	.04
Adverse prognostic factors for OS			
Refractory disease at transplantation	1.51	1.03 to 2.21	.003
Myeloablative conditioning	2.05	1.27 to 3.29	.04
Previous failed autologous transplantation	1.59	1.07 to 2.35	.02
Multivariate analysis restricted to RIC group			
TBI-based conditioning regimen	2.55	1.09 to 5.93	.03

Abbreviations: HL, Hodgkin's lymphoma; SCT, stem-cell transplantation; RIC, reduced-intensity conditioning; TBI, total-body irradiation; PFS, progression-free survival; OS, overall survival.

relapsed or refractory HL allografted from a matched related donor or MUD. The relatively large number of patients and the long follow-up (76 months for patients after standard conditioning and 73 months for patients after RIC) emphasizes the validity of the data presented, although this study, like other retrospective multicenter analyses, may have important shortcomings. Historically, the role of alloSCT in the management of patients with HL has been highly controversial. Our analysis clearly indicates that RIC significantly decreases NRM even in patients with poor prognostic features at the time of allograft. The 3-month and 1-year incidences of NRM were 15% and 23%, respectively, and compare favorably with data that had previously been reported by single-institution trials or trials with only a few participating institutions.[14,18,19] The decrease in NRM is even more impressive when we take into account the poor prognostic features of the RIC population. A retrospective analysis of the CIBMTR comparing 146 patients with relapsed HL treated with alloRIC versus 38 patients treated with a conventional allograft demonstrated no advantage for the RIC patients in terms of NRM, PFS, or OS.[25] Reasons for this discrepancy between both analyses are not clear but the low number of patients included in the myeloablative group in the CIBMTR analysis as well as the shorter follow-up could in part account for the discrepancy. Furthermore, the CIBMTR analysis was restricted to patients with MUD.

The reduction in NRM translated into a better OS and a trend for better PFS for the patients treated with RIC regimens. Despite the marginal improvement seen with RIC, long-term outcome is still disappointing. Chemotherapy-refractory disease and a previously failed ASCT was present in 60% of patients reported here and certainly contributed to the relatively poor outcome. At least three recent analyses have emphasized the role of chemotherapy sensitivity before alloSCT as a strong prognostic factor,[14,18,19] and it therefore would seem reasonable to try to reduce the tumor load as much as possible before transplantation. A double transplantation strategy (ASCT followed by alloRIC) has been proposed as an effective way to accomplish this goal.[15] However, whether this approach will overcome the intrinsic refractoriness of tumor cells to cytotoxic drugs requires additional study.

Anderlini et al[14] reported better OS and a trend for better PFS for HL patients allografted using a combination of fludarabine and melphalan compared with a less intensive protocol. In our analysis, low-dose TBI was an independent adverse prognostic factor for relapse, OS, and PFS after alloSCT. The group from the Fred Hutchinson Cancer Research Center (Seattle, WA) reported disappointing results in terms of relapse rate, OS, and PFS (50%, 39%, and 11%, respectively) at 1 year in 18 patients with HL treated with a combination of fludarabine and low-dose TBI (2 Gy).[17] If one accepts that mounting an effective graft-versus-HL reaction may require several months, preventing early progression by administering a vigorous conditioning regimen remains an essential goal to accomplish. In this sense, the combination of a more intensive preparative regimen, the BEAM protocol together with a profound T-cell depletion with alemtuzumab as aGVHD prophylaxis has been demonstrated to be associated with sustained donor engraftment, a high response rate, minimal toxicity (NRM, 7.6%), and a low incidence of GVHD.[20]

As in the United Kingdom cooperative group analysis,[18] we found that the use of a MUD or an HLA-identical sibling produced similar results in terms of PFS and OS. If alloRIC is to gain a role in the

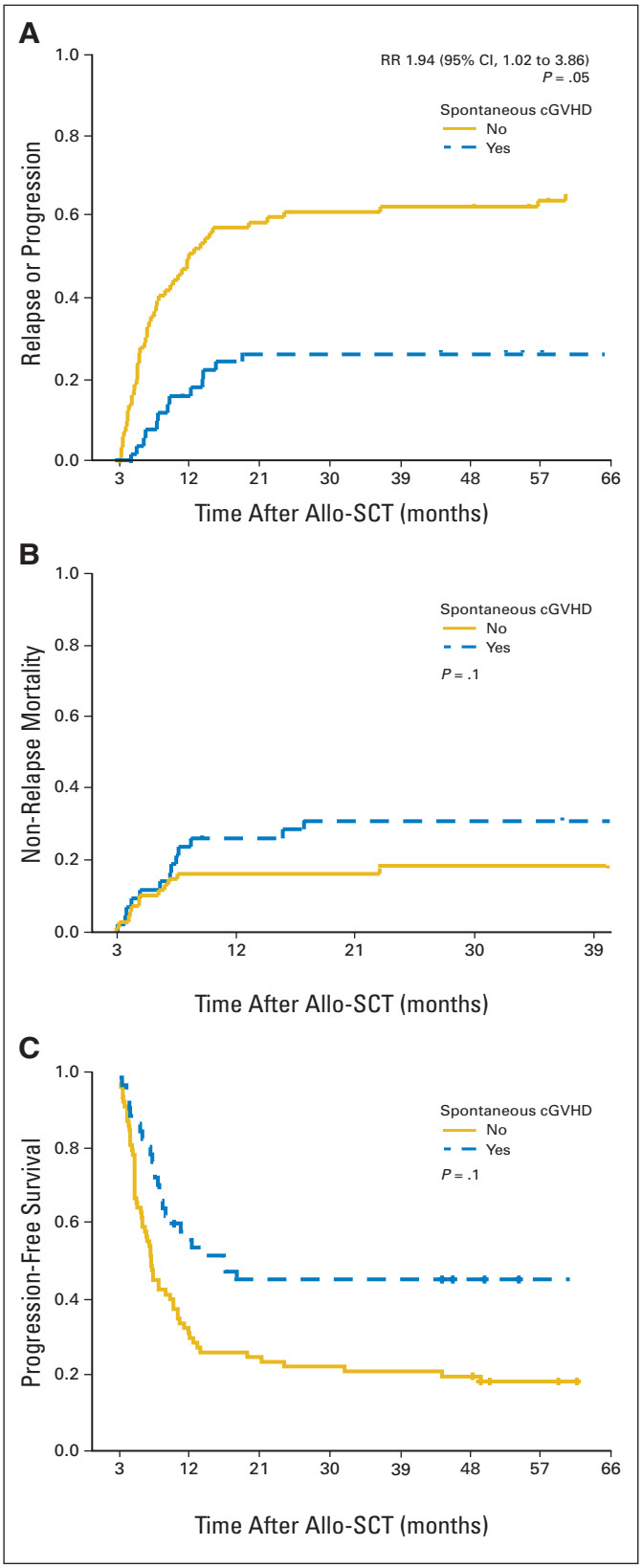

Fig 3. Influence of chronic graft-versus-host disease (cGVHD) in the outcome after allogeneic stem-cell transplantation (alloSCT), based on a landmark analysis. Relative risk (RR) and *P* values are from multivariate Cox models with cGVHD as a time-dependent covariate. Cumulative incidence of (A) relapse or progression, (B) nonrelapse mortality, and (C) Kaplan-Meier estimation of progression-free survival by the development of spontaneous cGVHD.

management of HL patients, the use of MUDs is essential to expand the number of patients eligible for the procedure.

Formal proof of a graft-versus-HL effect is not easy to accomplish. Milpied et al,[10] in a retrospective case-control study from the EBMT, and subsequently Peniket et al,[26] showed circumstantial evidence that a graft-versus-HL effect exists and is correlated to the occurrence of GVHD. Anderson et al[6] also reported a lower relapse rate in patients with HL who received an alloSCT compared with recipients of an ASCT, and Akpek et al[7] reported a trend toward lower relapse rates in patients who underwent alloSCT while in chemotherapy-sensitive relapse and in patients who developed cGVHD. RIC regimens may be more suitable to demonstrate the existence of a graft-versus-HL effect if the high and confounding NRM associated with conventional regimens is reduced. All published series reporting on alloRIC—although with lower numbers of patients and relatively short follow-up—indicated lower relapse rates in patients developing cGVHD after transplantation.[14,18,19] Furthermore, 40% to 50% of patients treated with donor lymphocyte infusions responded.[18,19] In our cohort of patients cGVHD had a significant impact on the long-term outcome because the relapse rate was significantly lower in patients developing cGVHD.

In conclusion, this study demonstrates that the use of RIC protocols significantly reduces NRM after alloSCT in HL patients who have experienced relapse. No significant increase of relapse rates after RIC was seen. Chemotherapy sensitivity at alloSCT and the extent of prior treatment were the major prognostic factors for both PFS and OS. Relapse remains the most important cause of treatment failure, after both RIC and myeloablative conditioning. Moreover, this analysis confirms the existence of a clinically significant graft-versus-HL tightly correlated with the development of cGVHD. Nevertheless, details of the transplantation procedure, such as the optimal conditioning regimen or the best GvHD prophylaxis, remain controversial. In this sense, alloSCT has to be considered an experimental modality to treat relapsed HL, and should only be performed within prospective clinical trials.[27]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).