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The Impact of Graft-versus-Host Disease on the Relapse Rate in Patients with Lymphoma Depends on the Histological Subtype and the Intensity of the Conditioning Regimen



Alvaro Urbano-Ispizua^{1,*}, Steven Z. Pavletic², Mary E. Flowers³, John P. Klein^{4,5}, Mei-Jie Zhang^{4,5}, Jeanette Carreras⁴, Silvia Montoto⁶, Miguel-Angel Perales⁷, Mahmoud D. Aljurf⁸, Görgün Akpek⁹, Christopher N. Bredeson¹⁰, Luciano J. Costa¹¹, Christopher Dandoy¹², César O. Freytes¹³, Henry C. Fung¹⁴, Robert Peter Gale¹⁵, John Gibson¹⁶, Mehdi Hamadani⁴, Robert J. Hayashi¹⁷, Yoshihiro Inamoto³, David J. Inwards¹⁸, Hillard M. Lazarus¹⁹, David G. Maloney³, Rodrigo Martino²⁰, Reinhold Munker²¹, Taiga Nishihori²², Richard F. Olsson^{23,24}, David A. Rizzieri²⁵, Ran Reshef²⁶, Ayman Saad¹¹, Bipin N. Savani²⁷, Harry C. Schouten²⁸, Sonali M. Smith²⁹, Gérard Socié³⁰, Baldeep Wirk³¹, Lolie C. Yu³², Wael Saber⁴

¹ Department of Hematology, Hospital Clinic, University of Barcelona, IDIBAPS, and Institute of Research Josep Carreras, Barcelona, Spain

² Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland

³ Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

⁴ Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

⁵ Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin

⁶ Department of Haemato-oncology, St. Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom

⁷ Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York

⁸ Department of Oncology, King Faisal Specialist Hospital Center and Research, Riyadh, Saudi Arabia

⁹ Section of Hematology Oncology, Banner MD Anderson Cancer Center, Gilbert, Arizona

¹⁰ The Ottawa Hospital Blood and Marrow Transplant Program and the Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

¹¹ Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama

¹² Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

¹³ South Texas Veterans Health Care System and University of Texas Health Science Center San Antonio, San Antonio, Texas

¹⁴ Department of Medical Oncology, Fox Chase Cancer Center, Temple Health, Philadelphia, Pennsylvania

¹⁵ Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom

¹⁶ Institute of Haematology, Royal Prince Alfred Hospital, Camperdown, Australia

¹⁷ Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St. Louis, St. Louis, Missouri

¹⁸ Division of Hematology, Mayo Clinic, Rochester, Minnesota

¹⁹ Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, Ohio

²⁰ Division of Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

²¹ Division of Hematology/Oncology, Department of Internal Medicine, Louisiana State University Health, Shreveport, Louisiana

²² Department of Medical Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

²³ Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

²⁴ Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden

²⁵ Division of Hematologic Malignancies and Cellular Therapy, Duke University, Durham, North Carolina

²⁶ Department of Medicine, Abramson Cancer Center, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

²⁷ Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

²⁸ Department of Hematology, Academische Ziekenhuis, Maastricht, Netherlands

²⁹ Section of Hematology/Oncology, University of Chicago, Chicago, Illinois

³⁰ Department of Hematology, Hôpital Saint Louis, Paris, France

³¹ Department of Internal Medicine, Stony Brook University Medical Center, Stony Brook, New York

³² Division of Hematology/Oncology, Center for Cancer and Blood Disorders, Children's Hospital/Louisiana State University Medical Center, New Orleans, Louisiana

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* Correspondence and reprint requests: Alvaro Urbano-Ispizua, Department of Hematology, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain.

E-mail address: aurbano@clinic.ub.es (A. Urbano-Ispizua).

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The purpose of this study was to analyze the impact of graft-versus-host disease (GVHD) on the relapse rate of different lymphoma subtypes after allogeneic hematopoietic cell transplantation (allo-HCT). Adult patients with a diagnosis of Hodgkin lymphoma, diffuse large B cell lymphoma, follicular lymphoma (FL), peripheral T cell lymphoma, or mantle cell lymphoma (MCL) undergoing HLA-identical sibling or unrelated donor hematopoietic cell transplantation between 1997 and 2009 were included. Two thousand six hundred eleven cases were included. A reduced-intensity conditioning (RIC) regimen was used in 62.8% of the transplantations. In a multivariate analysis of myeloablative cases ($n = 970$), neither acute (aGVHD) nor chronic GVHD (cGVHD) were significantly associated with a lower incidence of relapse/progression in any lymphoma subtype. In contrast, the analysis of RIC cases ($n = 1641$) showed that cGVHD was associated with a lower incidence of relapse/progression in FL (risk ratio [RR], .51; $P = .049$) and in MCL (RR, .41; $P = .019$). Patients with FL or MCL developing both aGVHD and cGVHD had the lowest risk of relapse (RR, .14; $P = .007$; and RR, .15; $P = .0019$, respectively). Of interest, the effect of GVHD on decreasing relapse was similar in patients with sensitive disease and chemoresistant disease. Unfortunately, both aGVHD and cGVHD had a deleterious effect on treatment-related mortality and overall survival (OS) in FL cases but did not affect treatment-related mortality, OS or PFS in MCL. This study reinforces the use of RIC allo-HCT as a platform for immunotherapy in FL and MCL patients.

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INTRODUCTION

A significant number of patients with lymphoma are not cured with conventional treatment or after high-dose therapy and autologous transplantation. Allogeneic hematopoietic cell transplantation (allo-HCT) is a potential curative procedure for these patients because of the antilymphoma effect of both the cytotoxic drugs in the conditioning regimen and the immune attack mediated by the donor's T cells. Unfortunately, the conventional myeloablative conditioning regimen (MAB) of allo-HCT is associated with high non-relapse mortality (NRM) and, as a result, its role in the therapeutic algorithm for lymphoma remains controversial [1]. Furthermore, the average age of patients with the most frequent subtypes of lymphoma is 60 to 65 years, an age when MAB transplantations have prohibitive NRM. Allo-HCT with a reduced-intensity conditioning (RIC) regimen is associated with a lower rate of mortality and now represents 80% of all allo-HCT in some types of lymphoma [2]. RIC allo-HCT transplantations would be an immunotherapy platform for different subtypes of lymphoma, if a potent graft-versus-lymphoma (GVLy) effect were demonstrated. The reported clinical evidence of a GVLy effect is less robust than that published for a graft-versus-leukemia effect. This may be because of the relatively limited number of allo-HCT lymphoma cases reported in most series, as well as the fact that different types of lymphoma are often analyzed together. The main objectives of this study were to determine if graft-versus-host disease (GVHD) was associated with a lower relapse rate in specific subtypes of lymphomas and to analyze whether this effect differs in MAB and RIC transplantations. We hypothesized that the different biological characteristics and growth kinetics between histological subtypes might have a different impact of GVHD on relapse rate. We also wanted to identify whether a potential decreased relapse rate in patients developing GVHD would result in an overall improved clinical outcome.

PATIENTS AND METHODS**Data Source**

The Center for International Blood and Marrow Transplant Research (CIBMTR) (formerly IBMTR) is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantations (HCT) to a centralized

statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable US federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in the CIBMTR capacity as a public health authority under the Health Insurance Portability and Accountability Act Privacy rule. Additional details regarding the data source are described elsewhere [3].

Patients

We analyzed 2611 cases of patients older than 18 years old who were undergoing HLA-identical sibling or unrelated-donor HCT for lymphoma reported to the CIBMTR between 1997 and 2009. Lymphoma types were categorized as Hodgkin lymphoma (HL) ($n = 466$), diffuse large B cell lymphoma (DLBCL) ($n = 579$), follicular lymphoma (FL) ($n = 871$), peripheral T cell lymphoma (PTCL) ($n = 195$), and mantle cell lymphoma (MCL) ($n = 500$). Patients who received cord blood and ex vivo T cell–depleted grafts were excluded.

Study Endpoints

The main goal of this study was to compare the association of GVHD with relapse rates in patients with different lymphoma subtypes and to analyze whether this association differs in MAB and RIC/nonmyeloablative (NMA) [4]. We also analyzed the impact of GVHD on NRM, overall survival (OS), and progression-free survival (PFS). *Acute* and *chronic GVHD* (aGVHD and cGVHD, respectively) were defined as the occurrence of grade II, III, or IV skin, gastrointestinal, or liver abnormalities that fulfill the consensus criteria of aGVHD [5] and limited and extensive cGVHD [6], respectively. *NRM* was defined as death after transplantation without relapse or progression, where relapse and progression were competing risks. Those patients who survived without recurrence or progression were censored at the time of last contact. *OS* was defined as time from transplantation to death. Death from any cause was considered an event. *PFS* was defined as survival after transplantation without recurrence or lymphoma progression. Recurrence or progression of the disease and death were counted as events. Those patients receiving donor lymphocyte infusions (DLI) were censored when receiving the first dose. Those patients who survived without recurrence or progression were censored at the time of last contact.

Statistical Analysis

Multivariate analyses were performed using Cox proportional hazards models. A stepwise model building approach was used to identify the significant risk factors associated with the outcomes of relapse/progression, NRM, PFS, and OS. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. When the test indicated differential effects over time (nonproportional hazards), models were constructed breaking the post-transplantation time course into 2 periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions were further tested. A backward stepwise model selection approach was used to identify all significant risk factors. The main-effect variable was defined as the time-dependent occurrence of aGVHD only versus aGVHD + cGVHD versus cGVHD only versus neither. Each step of model building included the main “treatment” effect. Factors that were significant at a level of 5%

were kept in the final model. The potential interactions between the main effect and all significant risk factors were tested. The effect of GVHD on the relapse rate with 95% confidence intervals (CI) were reported for each lymphoma subtype and compared between lymphoma subtypes. Variables considered in the multivariate models are as follows: patient-related (age at transplantation, sex, and Karnofsky performance status at transplantation), disease-related (lymphoma histology, disease stage at diagnosis, B symptoms at diagnosis, number of lines of chemotherapy before transplantation, disease status at transplantation, and rituximab before transplantation), and transplantation-related (interval from diagnosis to transplantation, prior autologous transplantation, interval from autologous to allogeneic, donor-recipient cytomegalovirus status, donor-recipient sex match, conditioning regimen, donor type, graft type, year of transplantation, antithymocyte globulin/alemtuzumab, and GVHD prophylaxis). To clarify whether the effect of GVHD on decreasing relapse if present was in both sensitive and chemoresistant cases, we performed a multivariate analysis in which the main variable of interest was GVHD and the main outcome was relapse/progression. If in the multivariate analysis, disease status independently influenced relapse/progression, we then performed an interaction analysis to see precisely whether GVHD had a different effect in the group of patients with sensitive disease versus those

patients with chemoresistant disease. A day 180 post-HCT landmark analysis method was also used to compute the cumulative incidence of relapse/progression in patients who had aGVHD and/or cGVHD versus without aGVHD or cGVHD.

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. The median patient age was younger for patients with HL, with a male predominance in MCL and PTCL. There were no differences with respect to the proportion of patients with chemosensitive versus chemoresistant disease. A higher proportion of patients with HL had undergone a prior autologous transplantation. More patients in the HL group had received an unrelated donor transplant compared with the rest of the patients. There were no differences in the use of antithymocyte globulin/alemtuzumab or in post-transplantation GVHD prophylaxis between lymphoma subgroups.

Table 1
Patient Demographics and Clinical Characteristics

Variable	HL	DLBCL	FL	PTCL	MCL
No. of patients	466	579	871	195	500
Age at transplantation, median (range), yr	32 (18-69)	49 (18-70)	49 (21-70)	45 (18-69)	56 (23-75)
Sex					
Male	278 (60)	338 (58)	506 (58)	139 (71)	411 (82)
Female	188 (40)	241 (42)	365 (42)	56 (29)	89 (18)
Karnofsky score					
<90%	138 (30)	221 (38)	245 (28)	76 (39)	145 (29)
≥90%	288 (62)	325 (56)	592 (68)	111 (57)	322 (64)
Missing	40 (9)	33 (6)	34 (4)	8 (4)	33 (7)
No. of prior chemotherapy lines, median	4	4	3	3	3
Rituximab before transplantation					
Yes	25 (5)	302 (52)	486 (56)	6 (3)	279 (56)
No	441 (95)	277 (48)	385 (44)	189 (97)	221 (44)
Disease status before transplantation					
Chemosensitive	287 (62)	339 (59)	589 (68)	126 (65)	359 (72)
Chemoresistant	166 (36)	202 (35)	243 (28)	61 (31)	108 (22)
Missing	13 (3)	38 (7)	39 (4)	8 (4)	33 (7)
Interval from diagnosis to transplantation, mo	36 (5-413)	20 (2-309)	38 (1-352)	13 (2-159)	26 (3-175)
Prior autologous transplantation					
No	155 (33)	431 (74)	775 (89)	170 (87)	405 (81)
Yes	311 (67)	148 (26)	96 (11)	25 (13)	95 (19)
Interval from autologous to allo, mo	36 (5-413)	20 (2-309)	38 (1-352)	13 (2-159)	26 (3-175)
Type of donor					
HLA-identical sibling	100 (21)	231 (40)	461 (53)	89 (46)	213 (43)
URD well-matched	219 (47)	218 (38)	254 (29)	69 (35)	202 (40)
URD partially matched	117 (25)	94 (16)	100 (11)	24 (12)	63 (13)
URD mismatched	24 (5)	22 (4)	19 (2)	5 (3)	8 (2)
UNR unknown	6 (1)	14 (2)	37 (4)	8 (5)	14 (3)
Conditioning intensity					
MAB	123 (26)	268 (46)	331 (38)	99 (51)	149 (30)
RIC	261 (56)	224 (39)	307 (35)	64 (33)	177 (35)
NMA	82 (18)	87 (15)	233 (27)	32 (16)	174 (35)
Graft type					
Bone marrow	115 (25)	153 (26)	216 (25)	33 (17)	92 (18)
Peripheral blood	351 (75)	426 (74)	655 (75)	162 (83)	408 (82)
Year of transplantation					
1997-2000	56 (12)	120 (21)	202 (23)	11 (6)	84 (17)
2001-2004	180 (39)	188 (32)	320 (37)	61 (31)	171 (34)
2005-2009	230 (49)	271 (47)	349 (40)	123 (63)	245 (49)
ATG/alemtuzumab					
ATG + alemtuzumab	1 (<1)	0	0	0	1 (<1)
ATG alone	119 (26)	126 (22)	144 (17)	35 (18)	103 (21)
Alemtuzumab alone	40 (9)	48 (8)	67 (8)	18 (9)	58 (12)
No ATG or alemtuzumab	304 (65)	389 (67)	649 (75)	139 (71)	324 (65)
Missing	2 (<1)	16 (3)	11 (1)	3 (2)	14 (3)
GVHD prophylaxis					
Tacrolimus ± others	273 (59)	312 (54)	444 (51)	107 (55)	259 (52)
Cyclosporine ± others	182 (39)	246 (42)	390 (45)	79 (41)	229 (46)
Other GVHD prophylaxis	11 (3)	21 (4)	37 (5)	9 (6)	12 (2)
Follow-up of survivors, median (range), mo	61 (3-170)	57 (3-170)	63 (3-175)	48 (3-161)	60 (3-168)

URD indicates unrelated donor; UNR, unrelated; ATG, antithymocyte globulin.

Table 2
Univariate Analyses^a

Outcomes	HL	DLBCL	FL	PTCL	MCL	P Value ^b
aGVHD	40 (36-44)	35 (31-39)	34 (31-37)	39 (32-46)	36 (32-40)	.208
cGVHD	47 (43-52)	33 (29-37)	45 (42-49)	49 (41-56)	43 (38-47)	<.001
NRM	41 (36-46)	47 (43-51)	36 (33-39)	38 (31-46)	43 (39-48)	.001
Relapse/progression	38 (34-43)	31 (27-34)	14 (12-17)	32 (25-39)	25 (21-29)	<.001
PFS	21 (17-25)	22 (19-26)	50 (47-54)	30 (23-37)	32 (27-36)	<.001 [†]
OS	29 (25-33)	24 (21-28)	56 (53-59)	37 (29-45)	41 (36-45)	<.001 [‡]

^a Probabilities of aGVHD (at 100 days), cGVHD (at 1 year), NRM and relapse/progression (both at 5 years) were calculated using the cumulative incidence estimate. PFS and OS (both at 5 years) were calculated using the Kaplan-Meier product limit estimate.

[†] Pointwise test.

[‡] Log-rank test.

Transplantation Outcomes

Transplantation outcomes are shown in Table 2. OS at 5 years was better for patients with FL and MCL than for those with HL and DLBCL. Similarly, 5-year PFS was better for those with FL compared with the rest of the patients (Figures 1 and 2). The 5-year cumulative incidence of relapse was also different between lymphoma subgroups (Figure 3). There was no significant difference between the lymphoma subgroups in the 100-day cumulative incidence of aGVHD grades II to IV. The rate of 1-year cGVHD was not significantly different for patients with HL, FL, PTCL, and MCL, but it was lower for those with DLBCL.

Association of acute and chronic GVHD on the Incidence of Relapse/Progression

We first examined the effects of GVHD in the entire cohort ($n = 2611$). In a multivariate analysis, cGVHD was associated with a lower risk of relapse/progression in MCL (risk ratio [RR], .41; 95% CI .21 to .80; $P = .009$), but not in the other lymphoma subtypes (Supplementary Table 1).

We next looked at the association of GVHD with relapse/progression in 2 different groups, according to the intensity of the conditioning regimen: MAB and RIC/NMA. In patients who underwent transplantation with MAB, neither aGVHD nor cGVHD were significantly associated with a lower risk of relapse/progression in any type of lymphoma. In contrast, in patients who underwent transplantation with RIC/NMA regimens ($n = 1641$), cGVHD was associated with a lower incidence of relapse/progression in those with FL (RR, .51; $P = .049$) and in those with MCL (RR, .41; $P = .019$). Patients with FL and MCL developing both aGVHD and cGVHD had the lowest risk of relapse (RR, .12; 95% CI, .03 to .49; $P = .003$, and RR, .14; 95% CI, .04 to .49; $P = .0019$, respectively) (Tables 3 and 4). We also analyzed the impact of GVHD on relapse rate

depending on whether the group was either chemosensitive or chemoresistant, which was performed for the overall group, for MAB, and for RIC transplantations. Of interest, the effect of GVHD on decreasing relapse was similar in patients with sensitive disease and chemoresistant disease (see interaction analysis results at the bottom of Tables 3 and 4).

To obtain a graphical illustration of the association of GVHD on relapse rate in RIC allo-HCT in FL and MCL, we performed a day 180 landmark study. Three hundred and sixty-seven of 540 FL cases and 208 of 351 MCL cases fulfilled the conditions of being alive and in remission at 180 days after transplantation. Results from the landmark analysis were very similar to those observed in the multivariate analysis, and, thus, those patients with FL and MCL developing both aGVHD and cGVHD had the lowest risk of relapse, those developing either aGVHD or cGVHD had an intermediate risk of relapse, and those patients developing neither aGVHD nor cGVHD had the highest risk of relapse (Figure 4).

Impact of acute and chronic GVHD on OS, NRM, and PFS

GVHD was reported as the primary cause of death in 13% of the cases in HL, 10% in DLBCL, 17% in FL, 13% in PTCL, and 15% in MCL (Table 5). In a time-dependent multivariate analysis, aGVHD was associated with inferior OS and NRM in all lymphoma subtypes. When analyzed in the 2 specific lymphoma groups in which GVHD was associated with lower relapse, ie, patients with FL and MCL who underwent RIC/NMA transplantations, both aGVHD and cGVHD had a deleterious effect on NRM and OS in FL cases and did not impact NRM, OS or PFS in MCL (Supplementary Table 2).

DISCUSSION

A potential clinical impact of GVHD in FL and MCL has been discussed in 2 recent reviews [1,7]. Two international

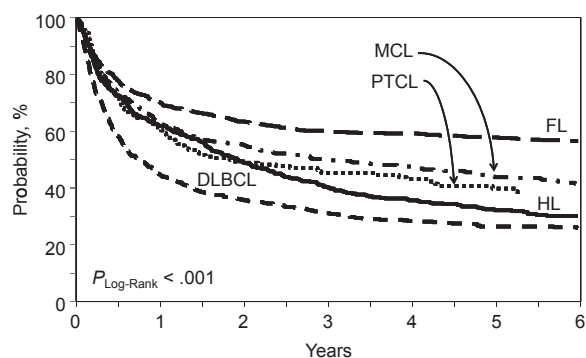


Figure 1. Overall survival of the different lymphoma subtypes, in the overall group.

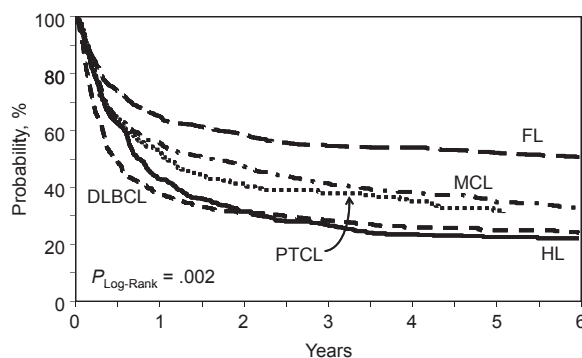


Figure 2. Progression-free survival of the different lymphoma subtypes, in the overall group.

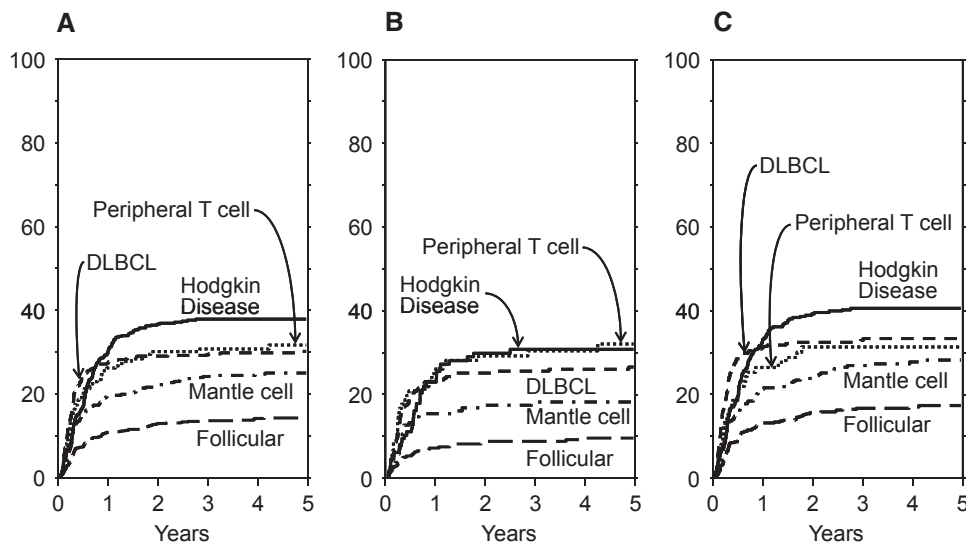


Figure 3. Cumulative incidence of relapse per lymphoma subtype in the overall group (A), in myeloablative conditioning (B), and in reduced-intensity conditioning (C).

registry series reported a lower relapse rate in patients with FL who underwent allo-HCT compared with those receiving an autologous HCT [8,9], but they did not find any association between aGVHD or cGVHD and recurrence after allo-HCT. Here we show, for the first time, in a very large series of FL

patients who underwent allo-HCT, an association between GVHD and a lower relapse rate. As far as MCL is concerned, 1 study [10] suggested a lower relapse rate after allo-HCT than after autologous HCT. In the univariate analysis, patients with cGVHD had a lower actuarial probability of relapse than

Table 3
Multivariate Analysis of the Influence of GVHD on Relapse/Progression in Mantle Cell and Follicular Lymphoma (acute GVHD II to IV)

Risk Factor	RR (95% CI)	P Value
MAB allo-HCT		
MCL (n = 149) [*]		
aGVHD II-IV	1.51 (.37-6.12)	.56
cGVHD	.42 (.08-2.19)	.30
aGVHD II-IV + cGVHD versus no GVHD	1.32 (.23-7.49)	.75
Disease status		
Sensitive	1.00	
Resistant	2.51 (1.02-6.18)	.05
Missing	3.12 (1.17-8.34)	.024
FL (n = 331) [†]		
aGVHD II-IV	.87 (.17-4.56)	.87
cGVHD	1.22 (.34-4.40)	.76
aGVHD II-IV + cGVHD versus no GVHD	1.34 (.35-5.10)	.67
Disease status		
Sensitive	1.00	
Resistant	3.20 (1.54-6.66)	.002
Missing	1.29 (.17-10.04)	.81
RIC/NMA allo-HCT [‡]		
MCL (n = 351)		
aGVHD II-IV	1.04 (.49-2.19)	.92
cGVHD	.41 (.20-.86)	.019
aGVHD II-IV + cGVHD versus no GVHD	.15 (.04-.50)	.002
Disease status		
Sensitive	1.00	
Resistant	1.96 (1.22-3.15)	.006
Missing	.15 (.02-1.06)	.057
FL (n = 540) [§]		
aGVHD II-IV	.46 (.16-1.28)	.14
cGVHD	.51 (.26-.99)	.049
aGVHD II-IV + cGVHD versus no GVHD	.14 (.03-.58)	.007

* Interaction test between GVHD disease status ($P = .79$). Three-degree freedom test.

[†] Interaction test between GVHD disease status ($P = .45$). Three-degree freedom test.

[‡] Interaction test between GVHD disease status ($P = .36$). Three-degree freedom test.

[§] Disease status was not significant.

Table 4
Multivariate Analysis of the Influence of GVHD on Relapse/Progression in Mantle Cell and Follicular Lymphoma (acute GVHD III and IV)

Risk Factor	RR (95% CI)	P Value
MAB allo-HCT [*]		
MCL (n = 149)		
aGVHD III-IV	1.66 (.33-8.41)	.54
cGVHD	.66 (.14-3.22)	.61
aGVHD III-IV + extensive cGVHD versus no GVHD	1.37 (.16-12.13)	.78
Disease status		
Sensitive	1.00	
Resistant	2.52 (1.03-6.17)	.044
Missing	3.17 (1.18-8.50)	.022
FL (n = 331) [†]		
aGVHD III-IV	1.47 (.40-5.44)	.56
cGVHD	.65 (.22-1.93)	.44
Disease status		
Sensitive	1.00	
Resistant	3.30 (1.58-6.90)	.002
Missing	1.21 (.16-9.35)	.86
RIC/NMA allo-HCT [‡]		
MCL (n = 351)		
aGVHD III-IV	.98 (.44-2.15)	.94
cGVHD	.27 (.11-.66)	.004
aGVHD III-IV + extensive cGVHD versus no GVHD	.20 (.05-.85)	.029
Disease status		
Sensitive	1.00	
Resistant	1.88 (1.16-3.04)	.010
Missing	.15 (.02-1.08)	.060
FL (n = 540) [§]		
aGVHD III-IV	.24 (.06-.99)	.049
cGVHD	.43 (.21-.87)	.018

* Interaction test between GVHD disease status ($P = .79$). Three-degree freedom test.

[†] Interaction test between GVHD disease status ($P = .45$). Three-degree freedom test.

[‡] Interaction test between GVHD disease status ($P = .36$). Three-degree freedom test.

[§] Disease status was not significant.

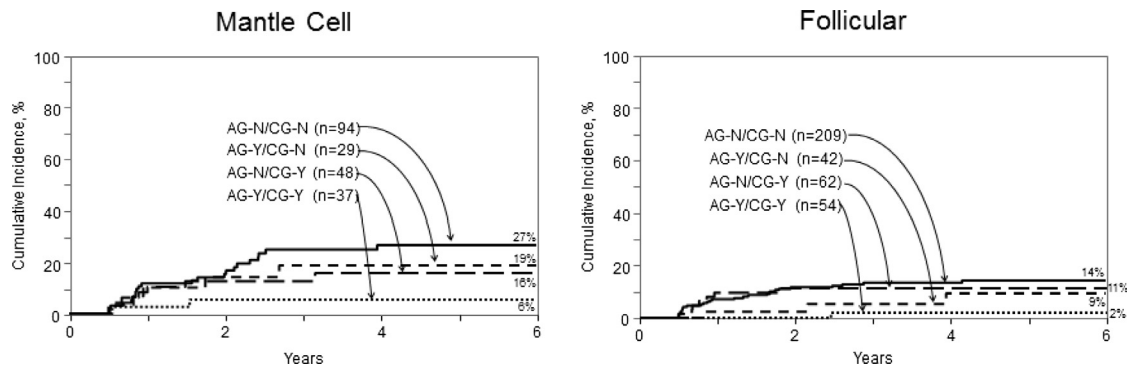


Figure 4. Landmark analysis at 180 days after RIC allo-HCT showing the cumulative incidence of relapse in patients who had: (1) no acute GVHD, no chronic GVHD (AG-N/CG-N); (2) acute GVHD, no chronic GVHD (AG-Y/CG-N); (3) no acute GVHD, chronic GVHD (AG-N/CG-Y); and (4) both acute GVHD and chronic GVHD (AG-Y/CG-Y) in (left) mantle cell lymphoma and in (right) follicular lymphoma.

those patients without this complication. However, a multivariate analysis was not performed, and competing risks were not taken into consideration. Here, we demonstrate a strong association of cGVHD with decreased relapse after allo-HCT for MCL analyzed in a multivariate study, considering cGVHD as a time-dependent variable. This is in line with studies showing a high relapse rate of MCL after allo-HCT when donor T cells are eliminated from the graft [11,12]. Thus, we suggest an important role of GVLY in reducing relapse rates in FL and MCL. A landmark analysis confirmed the effect of GVHD on the relapse rate in FL and MCL. Thus, as also was observed in the multivariate analysis, patients with FL and MCL developing both aGVHD and cGVHD had the lowest risk of relapse (Figure 4). Of interest, the effect of GVHD on decreasing relapse was similar in patients with sensitive disease and chemoresistant disease (Tables 3 and 4, interaction analysis).

An intriguing result from this study is that the association of GVHD and decreased relapse in FL and MCL lymphoma was observed only in allo-HCT performed with RIC/NMA regimens and not after MAB transplantations. One may speculate that the more intense MAB regimen already provides a significantly more cytotoxic, antilymphoma effect than the RIC/NMA regimen, making the addition of an allogeneic effect less obvious. From a clinical point of view, this disparity may have little relevance, as the vast majority of lymphoma patients now receive a RIC/NMA regimen as part of their allo-HCT. From a biological point of view, this peculiarity is difficult to explain because the effect of alloreactive

T cells developing both GVHD and GVLY should be similar, regardless of the intensity of the conditioning regimen. This difference might also be statistically justified. Thus, the initial smaller sample size for MAB transplantations than for RIC/NMA transplantations and the fact that more patients in the MAB group died early after allo-HCT may have led to a poorer detection of associations of GVHD and lower relapse. Similar observations of an association of GVHD on a decreasing relapse rate in RIC/NMA, but not in MAB allo-HCT, have also been described in acute myeloblastic leukemia and in myelodysplastic syndromes [13,14].

In this study we did not observe an association between GVHD and a lower rate of relapse in DLBCL. This is in line with previous studies showing that relapse after autologous HCT for DLBCL patients is quite similar to that after allo-HCT [15,16]. However, allo-HCT may be a salvage therapy for patients with DLBCL relapsing after an autologous HCT [17,18]. For HL, in 1996 the European Society for Blood and Marrow Transplantation (EBMT) published a report showing a lower relapse rate after MAB allo-HCT than after autologous HCT, but this was offset by a very high NRM associated with MAB [19]. More recently, in a multivariate analysis, the EBMT has not found an association of GVHD with relapse rate in patients with HL who underwent RIC [20], although in a landmark analysis, patients with cGVHD had a lower incidence of relapse. In the present study, which included a much larger number of patients, we did not observe an association of GVHD with a lower relapse rate in those with HL using a Cox model, in line with the EBMT results. If these

Table 5
Causes of Death

Cause of Death	HL	DLBCL	FL	PTCL	MCL
No. of deaths	331	433	403	112	293
Graft rejection	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Infection	46 (14)	70 (16)	80 (20)	22 (20)	49 (17)
Ipn	9 (3)	22 (5)	24 (6)	3 (3)	9 (3)
ARDS	7 (2)	12 (3)	10 (2)	1 (1)	12 (4)
GVHD	44 (13)	43 (10)	69 (17)	15 (13)	43 (15)
Primary disease	147 (44)	187 (43)	79 (20)	41 (37)	90 (31)
Organ failure	33 (10)	58 (13)	67 (17)	20 (18)	43 (15)
Second malignancy	2 (1)	1 (<1)	12 (3)	0	6 (2)
Hemorrhage	8 (2)	11 (3)	10 (2)	4 (4)	11 (4)
Accidental death	1 (<1)	0	2 (<1)	0	2 (1)
Vascular	6 (2)	2 (<1)	6 (1)	2 (2)	5 (2)
Toxicity	10 (3)	9 (2)	18 (4)	1 (1)	10 (3)
Other: not specified/unknown	17 (5)	17 (4)	25 (6)	3 (3)	12 (4)

Ipn indicates interstitial pneumonia; ARDS, acute respiratory distress syndrome.

results are confirmed in other studies, allo-HCT for DLBCL and HL should be only offered within the context of a clinical trial designed to improve the GVly effect. As far as PTCL is concerned, we were not able to demonstrate a relationship between GVHD and a lower rate of relapse. The low number of patients with this disease included in the study precludes us from drawing firm conclusions.

The association of GVHD with lower relapse rate herein observed in FL and MCL, but not in DLBCL, HL, and PTCL, are in line with results observed in short series of lymphoma patients treated with DLI. There are at least 3 studies showing a potent effect of DLI to treat FL and MCL relapses after allo-HCT [12,21,22]. In contrast, DLI seem to have very limited activity as a salvage treatment for patients with DLBCL relapsing after allo-HCT [23]. Results of DLI in HL and PTCL [16,24,25] are more encouraging, without achieving the excellent results obtained in FL and MCL lymphoma. Thus, DLI is very effective in FL and MCL, of moderate effect in HL and PTCL, and very limited in DLBCL. These, together with our own results, support the presence of a strong GVly effect after allo-HCT in FL and MCL. The low proliferation rate of indolent lymphomas might be 1 reason that explains an effective role of the donor's immune system to control tumor growth in these lymphoma subtypes.

The beneficial effect of GVHD on a lower relapse rate in FL and MCL did not translate into an overall clinical outcome advantage. This negative impact of GVHD, despite decreasing the relapse rate, as has been reported in other diseases [14,26]. Strategies combining attenuation of GVHD with post-HCT treatment maintenance and potentiating the GVly effect, with late DLI or chimeric antigen receptor–modified T cells [27], could improve the clinical outcome of FL and MCL patients undergoing RIC allo-HCT.

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SUPPLEMENTARY DATA

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