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Long-term outcomes after reduced-intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: a survey by the French Society of Bone Marrow Graft Transplantation and Cellular Therapy (SFGM-TC)

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ABSTRACT

Background and Objectives

High-dose chemotherapy with allogeneic stem cell transplantation (SCT) has proven to be a successful treatment for low-grade lymphoma (LGL), but is associated with considerable transplant-related mortality (TRM). In an effort to reduce toxic mortality while maintaining the graft-versus-leukemia effect, allogeneic SCT has been combined with a reduced-intensity conditioning (RIC) regimen. The aim of this study was to determine the outcome of patients with LGL treated with RIC allogeneic SCT.

Design and Methods

This retrospective multicenter study included 73 patients with relapsed or refractory LGL allografted after a RIC regimen between 1998 and 2005 whose data were recorded in a French registry.

Results

Patients received a median of three lines of therapy prior to RIC allogeneic SCT. The most widely used conditioning regimens were fludarabine + busulfan + antithymocyte globulin (n=43) and fludarabine + total body irradiation (n=21). Prior to allografting, patients were in complete response (CR; n=21), partial response (PR; n=33) or had chemoresistant disease (n=19). The median follow-up was 37 months (range, 16 to 77 months). In patients in CR, PR and chemoresistant disease, the 3-year overall survival rates were 66%, 64% and 32%, respectively, while the 3-year event-free survival rates were 66%, 52% and 32%, respectively. The 3-year cumulative incidences of TRM were 32%, 28% and 63%, respectively. The incidence of relapse was 9.6%.

Interpretation and Conclusions

Although associated with significant TRM, RIC allogeneic SCT in advanced chemosensitive disease leads to long-term survival.

Key words: RIC allogeneic transplantation, low-grade lymphoma.

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Low-grade lymphomas (LGL) are chemosensitive neoplasms characterized by a relentless succession of remissions and relapses when treated with conventional chemotherapy. The successive periods of remission are of shorter duration and patients invariably die of their disease. Data from three randomized studies provide no evidence that high-dose chemotherapy (HDT) with autologous stem cell transplantation (SCT) performed in first remission improves the survival.[1,2,3] The situation seems to be different in patients with relapsed disease as HDT with autologous SCT improved both relapse-free and overall survival rates when compared to conventional chemotherapy in a randomized trial.[4] However, even in this trial, only half of the patients achieved prolonged lymphoma-free survival after HDT with autologous SCT.

As a consequence of these findings, HDT with allogeneic SCT has been investigated as an additional therapeutic option in younger patients. The efficacy of this strategy is enhanced by the supportive presence of a graft-versus-lymphoma (GVL) effect in chronic lymphoproliferative diseases.[5] Van Besien *et al.*[6] reported rates of 3-year disease-free survival (DFS), overall survival (OS) and incidence of relapse of 49%, 49% and 16%, respectively, after allogeneic SCT with a myeloablative conditioning regimen. They also documented a transplant-related mortality (TRM) rate of 40% which was explained in part by the advanced state of the disease in the patients in their series. These results were updated in a study that reported rates of 3-year DFS, OS, incidence of relapse and TRM of 48%, 54%, 21% and 28%, respectively.[7] Other studies with myeloablative conditioning regimens have reported comparable rates of TRM.[8-11] In an effort to reduce toxic mortality while still exploiting the benefits of the GVL effect, recent studies have combined allogeneic SCT with a reduced-intensity conditioning (RIC) regimen. However, it is difficult to draw conclusions from these reports as they are somewhat limited in scope by either small population sample,[12] short follow-up,[13] or heterogeneity in the disease histologies.[14] We, therefore, conducted a retrospective multicenter study of the outcome of RIC-allogeneic SCT in 73 patients with LGL whose data were recorded in the registry of the *Société Française de Greffe de Moelle Osseuse et de Thérapie Cellulaire* (SFGM-TC).

Design and Methods

Selection of patients

The selection criteria included adults patients with LGL treated with a RIC regimen followed by allogeneic SCT performed between January 1998 and June 2005. Patients with transformed LGL, chronic lymphocytic leukemia or mantle cell lymphoma were excluded. Information concerning donors, recipients, graft harvesting and follow-up procedures were collected by transplant centers using prospectively designed forms. Seventy three patients from 19 transplant centers were identified and included in the present study. Retrospective diagnostic slide reviews were not performed and molecular biology data were unavailable. Information about performance status, chimerism evolution and donor lymphocyte infusions were also unavailable for the majority of patients.

Evaluation of response

Response was evaluated in accordance with the standardized response criteria for non-Hodgkin's lymphoma as reported by Cheson *et al.*[15] Complete response (CR) was defined as the complete disappearance of all detectable clinical, pathologic (i.e. bone marrow), and radiographic evidence of disease, all disease-related symptoms as well as the normalization of all biochemical abnormalities. Partial response (PR) was defined as ≥50% decrease of all measurable lesions. Stable disease (SD) was defined as no response or a response < 50%. Progressive disease (PD) was defined as at least a 50% increase of any measurable lesion or appearance of any new lesion during or at the end of therapy. Relapse was defined as appearance of any new lesion in patients who had achieved a CR.

Patients' general and transplant-related characteristics

The patients' characteristics are summarized in Table 1. A median number of 6×10^6 CD34$^+$ cells/kg (range, 1.3 to 21.8×10^6) were injected (peripheral blood stem cells: 7.3×10^6 CD34$^+$ cells/kg; range, 1.4 to 21.8×10^6 and bone marrow stem cells: 2.8×10^6 CD34$^+$ cells/kg; range, 1.3 to 5.5×10^6). Engraftment failed in two patients who died 2 months after transplantation from disseminated fungal infection and multi-organ failure. Median times to reach 0.5×10^9 neutrophils/L, 20×10^9 platelets/L and 50×10^9 platelets/L were 14 days (range, 6 to 33 days), 10 days (range, 0 to 232 days) and 14 days (range, 9 to 236 days), respectively. The two most widely used conditioning regimens were fludarabine + busulfan + antithymocyte globulin (ATG) [fludarabine 30 mg/m^2 per day (days -4, -3, -2, -1) with oral busulfan 0.5 mg/kg x 4 per day (days -4, -3, -2, -1) with rabbit ATG 2.5 mg/kg/day (days -4, -3] and fludarabine + total body irradiation (TBI) [fludarabine 30 mg/m^2 per day (days -4, -3, -2) with 2 Gy of TBI on day 0]. Graft-versus-host disease (GvHD) prophylaxis consisted of cyclosporine A (CsA) alone (5 to 6.25 mg/kg given orally twice a day) or CsA + mycophenolate mofetil (MMF, 15mg/kg per day given orally twice or three times a day) or CsA + methotrexate on day +1 (15 mg/m^2), +3 (10 mg/m^2), and +6 (10 mg/m^2). Intravenous formulations of CsA and MMF were administered to patients who were not able to tolerate oral medications. The multicenter nature of this study precludes the identification of a single pattern for tapering GvHD prophylaxis in patients not developing acute GvHD.

Table 1. General and transplant-related characteristics of the study population (n=73).

	No.	*%*
Time from diagnosis to alloSCT, months		
Median	46	
Range	6-284	
Prior lines of therapy		
1	4	5.5
2	30	41.1
3	20	27.4
>3	19	26
Prior autoSCT		
Yes	25	34.2
No	48	63.8
Disease status at alloSCT		
Complete response	21	28.8
Partial response	33	45.2
Stable disease	7	9.6
Progressive disease	12	16.4
Conditioning regimen		
Fluda + Bus + ATG	43	59
Fluda + TBI	21	28.7
Fluda + EDX	3	4
EDX + ATG	2	2.7
Fluda + Ida + Ara-C	1	1.4
Fluda + MoAbsCD20	1	1.4
Fluda + Melphalan	1	1.4
Fluda + BEAM	1	1.4
Source of stem cells		
Peripheral blood	59	80.8
Bone marrow	14	19.2
Donor		
Matched related	63	86.3
Matched unrelated	7	9.6
Mismatched related	1	1.4
Mismatched unrelated	2	2.7
GvHD prophylaxis		
Cyclosporine A alone	32	43.8
Cyclosporine A + MMF	25	34.2
Cyclosporine A + Methotrexate	16	22

AlloSCT: allogeneic stem cell transplantation; autoSCT: autologous stem cell transplantation; Fluda: fludarabine; Bus: busulfan; ATG: antithymocyte globulin; TBI: total body irradiation; EDX: endoxan; Ida: idarubicin; MoAbsCD20, anti-CD20 monoclonal antibody; BEAM, BCNU + etoposide + Ara-C + melphalan; GvHD: graft-versus-host disease; MMF: mycophenolate mofetil; Metho: methotrexate.

Statistical analysis

Univariate analysis was utilized to assess whether overall survival (OS), event-free survival (EFS) and TRM were affected by the number of lines of therapy received prior to allogeneic SCT or by the status of the disease at the time of the transplant. Prior lines of therapy were distributed as follows: one line (n=4, group 1), two lines (n=30, group 2), three lines (n=20, group 3), more than three lines (n=19, group 4). Groups 1 and 2 were combined because of the small number of patients in group 1. Comparisons were conducted between the three resultant groups: groups 1+2, group 3 and group 4. A similar reasoning was applied to the disease status which was distributed as follows: CR (n=21, group 1), PR (n=33, group 2), SD (n=7, group 3), PD (n=12, group 4). In this instance, the number of patients in group 3 was small. Groups 3 and 4 were therefore combined and comparisons were conducted between group 1, group 2 and groups 3+4 the latter of which was also the group of patients with chemoresistant disease.

Overall survival was calculated from the date of transplantation to either the date of death from any cause or last follow-up. Event-free survival was calculated from the date of transplantation to the date of relapse, progression, death from any cause or last follow-up. Transplant-related mortality included all causes of death other than disease relapse or progression occurring at any time after transplantation. Survival estimates were determined using the Kaplan and Meier method and compared by the log-rank test (univariate analysis) or by the Cox proportional hazards regression model (multivariate analysis). In the univariate analyses, GvHD was studied as a time-dependent covariate in a Cox model. Probabilities of GvHD, relapse and TRM were calculated by using cumulative incidence functions to allow for competing risks. Relapse and death without relapse were considered as competing risks for TRM and relapse, respectively. Relapse and death were considered as competing risks for GvHD. A Cox regression model was used to compare TRM and relapse hazards. Variables included in the univariate analyses were age (≥ *vs* <50 years), histology (follicular *vs* non-follicular), number of prior lines of therapy, chemoresistance, severe acute GvHD (grades III + IV), chronic GvHD, donor (related *vs* unrelated), conditioning regimen (ATG *vs* no ATG and fludarabine + TBI *vs* others), prior autologous SCT, and source of stem cells (peripheral blood *vs* bone marrow). Variables showing a p value <0.2 in the univariate analyses were entered in a multiple Cox model and sequentially removed from the model if they were not significantly associated with the outcome at the 0.05 level.

Results

Patients' characteristics

The median age of the population was 51 years (range, 33 to 66 years). Sixty-two percent of patients were male. The predominant histology was follicular (n=61). Other histologies were lymphoplasmacytoid (n=5), lymphocytic (n=4), and marginal zone B cell (n=3). Seventy-one patients were transplanted because of relapsed disease. Among these patients, 21 were in CR at the time of allogeneic SCT, while 33 were in PR, 6 had SD and 11 had PD. Two patients never achieved a complete or partial response during the course of their disease and were thus considered as having primary refractory at the time of alloSCT (one with SD, one with PD).

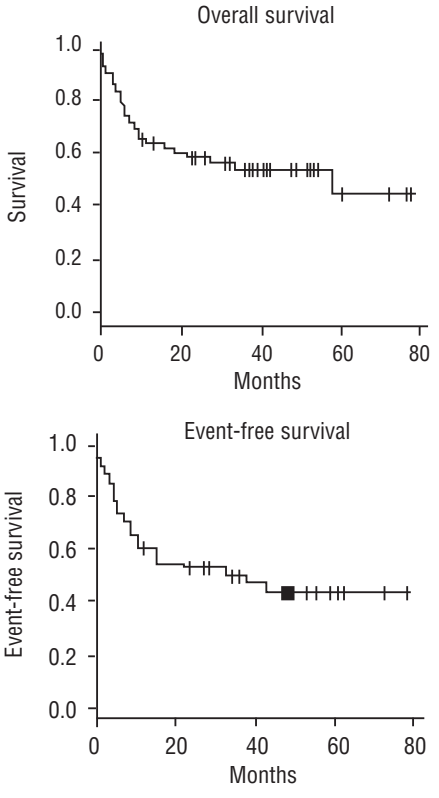

Figure 1. Overall survival and event-free survival of the study population (n=73).

Table 2. Causes of death in the study population.

	*Less than 100 days** (n=10)	*More than 100 days** (n=19)
Lymphoma progression n=3		
Transplant-related causes n=29		
Multi-organ failure	2	1
Acute GvHD	4	2
Chronic GvHD	/	1
Bacterial infection	1	4
Fungal infection	1	2
Hemorrhage	1	3
Encephalitis	1	1
Interstitial pneumonitis	0	2
Hepatitis	0	1
Unknown	0	2

**Days post-transplantation; GvHD: graft-versus-host disease.*

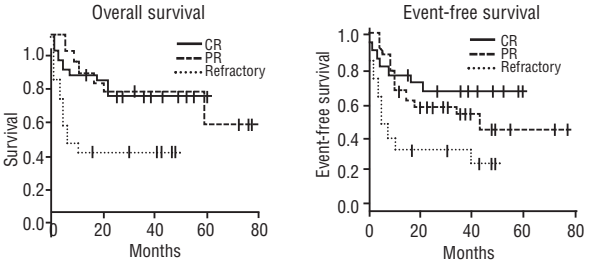

Figure 2. Overall survival and event-free survival according to the status of disease at the time of allogeneic stem cell transplantation. CR: complete response group (n=21): PR: partial response group (n=33); refractory: stable + progressive disease group (n=19).

Survival

The median follow-up of surviving patients was 37 months (range, 12 to 77 months). Three-year OS and EF rates were 56% (95% CI, 45% to 69%) and 51% (95% CI, 40% to 64%), respectively (Figure 1). Thirty two patients died by a median time of 6 months after allogeneic SCT (range, 1 to 58 months). The causes of death are presented in Table 2. The number of lines of therapy prior to allogeneic SCT did not affect either OS or EFS. However, patients with chemoresistant disease had significantly worse OS and EFS than patients with chemosensitive disease (CR or PR). As shown in Figure 2, the 3-year OS rates in CR, PR and chemoresistant patients were 66%, 64% and 32%, respectively (p=0.001) while the 3-year EFS rates in the same patients were 66%, 52% and 32%, respectively (p=0.003). Univariate analysis determined that OS was also adversely affected by unrelated donor and the development of severe acute GvHD, while EFS was also adversely affected by severe acute GvHD and conditioning regimen other than Fludarabine+TBI. Multivariate analysis (Table 3) indicated that both OS and EFS rates were adversely affected by chemoresistance and severe acute GvHD.

Transplant-related mortality

As shown in Figure 3, the 3-year TRM was 40% (95% CI, 28% to 51%). TRM rates at 100 days, 1 year and 2 years were 9%, 32% and 37%, respectively. Twenty-nine patients died of causes other than relapse at a median time of 5 months after allogeneic SCT (range, 1 to 34 months). The causes of TRM before and after day 100 are detailed in Table 2. The number of lines of therapy prior to SCT did not affect TRM. As shown in Figure 4, patients with chemoresistant disease had a significantly higher 3-year TRM (63%) than patients who achieved CR (32%) or PR (28%) (p=0.005). Univariate analysis indicated that severe acute GvHD and grafts from unrelated donors were also predictors of higher TRM. Indeed, the nine patients affected by grade III (n=4) or IV (n=5) acute GvHD died of causes other than relapse (refractory GvHD: n=6, bacterial infection: n=2, hemorrhage: n=1) at a median time of 5 months after allogeneic SCT. Multivariate analysis (Table 3) indicated that chemoresistance and severe acute GvHD adversely affected TRM. The year of transplant was not found to be significantly associated with TRM (*data not shown*). Table 4 shows that three or more lines of therapy were administered prior to allogeneic SCT to 74% of patients with chemoresistant disease and to 46% of patients with chemosensitive disease (p=0.04). An unrelated donor was used in 32% and 6% of these same patients, respectively (p=0.003).

Table 4. Comparison of patients with chemosensitive disease (CR+PR) and patients with chemoresistant disease (SD+PD).

	Chemosensitive (n=54)	*Chemoresistant (n=19)*	*p**
Median age (range)	51** (37-61)	51 (33-66)	0.4
Transplant period			0.2
1998-2001	23 (43%)	10 (53%)	
2002-2005	31 (57%)	9 (47%)	
Previous lines of therapy			0.04
< 3	29 (54%)	5 (26%)	
≥3	25 (46%)	14 (74%)	
Unrelated donor	3 (6%)	6 (32%)	0.003

*CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease. *χ^2 test, ** years.*

Table 3. Results of multivariate analysis.

Outcome	*Variable*	*HR*	*CI (95%)*	*p value*
OS	chemoresistance	2.9	1.3 to 6.5	0.009
OS	acute GvHD	5.8	2.4 to 13.9	< 0.001
EFS	chemoresistance	2.6	1.3 to 5.5	0.009
EFS	acute GvHD	4.6	2 to 10.7	< 0.001
TRM	chemoresistance	2.9	1.3 to 7	0.01
TRM	acute GvHD	6.9	2.7 to 17.8	< 0.001

OS: overall survival; EFS: event-free survival; TRM: transplant-related mortality; HR: hazards ratio; CI: confidence interval. Only variables that were statistically significant in the multivariate analysis are given. For OS and EFS, the variables included in the multivariate analysis were chemoresistance, acute GvHD (grades III + IV), chronic GvHD, fludarabine + TBI conditioning regimen, and unrelated donor. For TRM, the variables included in the multivariate analysis were chemoresistance, acute GvHD (grades III + IV), chronic GvHD, unrelated donor, fludarabine + TBI conditioning regimen and prior autologous stem cell transplantation.

Graft-versus-host disease

Acute GvHD occurred in 34 patients (grade I, n=9; grade II, n=16; grade III, n=4; grade IV, n=5) at a median time of 30 days after transplantation (range, 5 to 135 days). The incidences of grades II to IV and grades III + IV acute GvHD were 34% and 12%, respectively. Chronic GvHD occurred in 31 patients (limited, n=16; extensive, n=15) at a median time of 6 months after transplantation (range, 1 to 20 months). At 20 months, the cumulative incidences of chronic GvHD and of extensive chronic GvHD were 43% (95% CI, 31% to 54%) and 20% (95% CI, 11% to 30%), respectively. Both incidences remained constant at 5 years.

Relapse or progression

The 3-year cumulative incidence of relapse or progression was 9.6% (95% CI, 2.8% to 16.5%; Figure 3). Five patients relapsed at 10, 10, 16, 38, and 43 months. Four patients progressed at 3, 4, 4, and 9 months. Univariate analysis was unable to identify a predictor of lower risk of relapse.

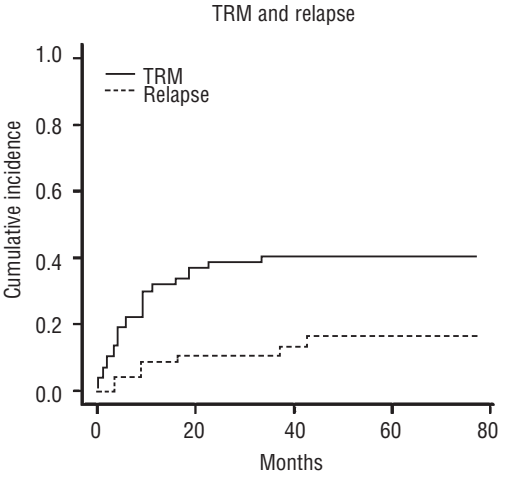

Figure 3. Cumulative incidences of transplant-related mortality (TRM) and relapse of the study population (n=73).

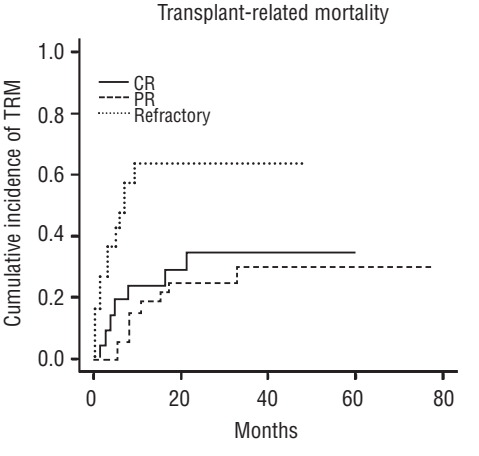

Figure 4. Transplant-related mortality according to the status of disease at the time of allogeneic stem cell transplantation. CR: complete response group (n=21); PR: partial response group (n=33); refractory: stable + progressive disease group (n=19).

Discussion

This study reports the outcome of 73 patients with relapsed or refractory LGL with a median follow-up of 37 months after RIC allogeneic SCT. The transplants were performed in 19 transplant centers in France between 1998 and 2005. This is the largest study with the longest follow-up period conducted in patients with LGL treated with RIC-allogeneic SCT. Fifty-nine percent of the patients received the fludarabine + busulfan + ATG conditioning regimen as reported by Slavin *et al.*[16] The use of this regimen was not linked to the use of unrelated donors as only 12% of patients received grafts from such a donor. Most patients were heavily pre-treated and one quarter had chemoresistant disease at transplantation, indicating a population

Table 5. Results of studies on allogeneic stem cell transplantation after a reduced-intensity conditioning regimen in patients with low-grade lymphoma.

	Khouri IF et al.,[12] 2001	*Robinson SP et al.,[13] 2002*	*Morris E et al.,[14] 2004*	*Maris MB et al.,[17] 2005*	*Present study*
Number of patients	20	52	41	45	73
Median age (years)	51	46	48	54	51
Median follow-up (months)	21	9	36	24	37
Prior lines of therapy	2	3	3	NA	3
Prior autoSCT	5%	29%	37%	33%	34%
Chemosens/chemores	90%/10%	85%/10%*	97%/3%	63%/24%**	74%/26%
Overall survival	84% (at 2 years)	65% (at 2 years)	73% (at 3 years)	58% (at 2 years)	56% (at 3 years)
Event-free survival	84% (at 2 years)	54% (at 2 years)	65% (at 3 years)	51% (at 2 years)	51% (at 3 years)
Relapse/progression	0%	21% (at 2 years)	44% (at 3 years)	15% (at 2 years)	9.6% (at 3 years)
100-day TRM	10%	11.5%	2%	NA	9%
2-year TRM	NA	30.9%	11%	34%	37%

*NA: not available; autoSCT, autologous stem cell transplantation; chemosens: chemosensitive disease; chemores: chemoresistant disease; TRM: transplant-related mortality. * untested relapse: 5%; **untested relapse: 13%.*

at a high risk of relapse. In these conditions, we report 3-year lymphoma-free survival rates of 66%, 52% and 32% in patients with CR, PR and chemoresistant disease, respectively, with a low incidence of relapse. The incidence of TRM in patients with chemosensitive disease (CR+PR) was half that in patients with chemoresistant disease. The overall incidence of grades II-IV acute GvHD was 34% and is most likely explained by the advanced median age of our patients (51 years). Moreover, grades II-IV acute GvHD occurred at a median time of 35 days post-transplantation which is after the protective effect of ATG had abated. Multivariate analysis indicated that OS, EFS and TRM rates were all adversely affected by chemoresistance and severe acute GvHD.

The first reports on the use of allogeneic SCT after a myeloablative conditioning regimen in patients with relapsed or refractory LGL showed that prolonged lymphoma-free survival could be obtained in about half of patients, with TRM ranging from 20 to 30%.[7-11] Afterwards, RIC-allogeneic SCT, which is used in patients on average 10 years older, was evaluated as an alternative strategy to reduce the toxicity while sparing the GVL effect. The results of the present study and of four others on RIC-allogeneic SCT in patients with relapsed or refractory LGL are presented in Table 5.[12-14,17] Patients had comparable median ages ranging from 46 to 51 years. They were all heavily pre-treated with a median of two to three lines of previous therapy. One third of the patients had undergone a previous autologous SCT, except in Khouri's series. Although the two studies by Robinson*et al.*[13] and Maris *et al.*[17] differ from our study, with shorter follow-up periods and higher incidences of relapse, they also reported similar survivals and incidences of TRM. These two studies, combined with our report, indicate that 2 to 3-year lymphoma-free survival rates of 51-54% and TRM of 31-40% can be expected after RIC-allogeneic SCT in patients with relapsed or refractory LGL. It remains unclear from these results whether the RIC regimen substantially reduces the TRM when compared to the myeloablative conditioning regimen.[7-10] These findings suggest instead that TRM is delayed rather than truly decreased as indicated in Table 5 by the higher incidences of TRM at 2 years than at 100 days. Such a pattern of delayed TRM is not disease-specific since it has also been reported in high-grade lymphoma[13] and Hodgkin's disease.[18] Collectively, these data highlight the importance of long follow-up periods for the analysis of TRM after RIC-allogeneic SCT and also underline the need for comparisons between RIC and myeloablative conditioning regimens.

Better results were reported by Khouri *et al.*[12] in a study with a short follow-up and a smaller number of patients. The first 11 patients received fludarabine and cyclophosphamide as a conditioning regimen while the nine subsequent patients received the same regimen plus rituximab at a dose of 375 mg/m^2 IV on day – 6 before transplantation and 1000 mg/m^2 IV on days 1, 8 and 15 after transplantation. A recently published abstract updated these findings in a study consisting of 47 patients with a median follow-up of 34 months. The updated results were a 3-year OS and EFS of 88%

and 85%, respectively.[19] Using a different strategy with *in vivo* T-cell depletion, Morris *et al*. reported their experience with a conditioning regimen comprising fludarabine, melphalan and alemtuzumab.[14] In this study, patients with a relapse, progressive disease, minimal residual disease or mixed chimerism at 6 months were given donor lymphocyte infusions. All patients but one had chemosensitive disease at transplantation. In our study, patients with chemosensitive disease (CR+PR) had 3-year OS, EFS, TRM and incidence of relapse of 65%, 58%, 31% and 11%, respectively. These results indicate that comparable OS and EFS rates can be obtained in patients with a chemosensitive disease whether or not a T-cell depletion strategy is adopted. However, Morris *et al*. reported a higher incidence of relapse and a lower TRM compared to our study. Collectively, these data suggest that allogeneic SCT after a RIC regimen including alemtuzumab in patients with chemosensitive LGL is associated with a reduced TRM, a higher risk of relapse and similar survival rates when compared to those after allogeneic SCT with a T-cell replete RIC regimen.

There is now evidence from randomized studies that rituximab combined with chemotherapy improves the outcome of patients with follicular lymphoma.[20,21] Moreover, several studies have reported that maintenance treatment with rituximab improves response duration and survival.[22-25] These interesting results raise the possibility that rituximab may also improve the outcome of RIC-allogeneic SCT in patients with follicular lymphoma. Khouri *et al*. adopted such a transplant strategy with the supposition that the administration of rituximab in the conditioning regimen and after RIC-allogeneic SCT might improve patients' outcome by affording better control of the disease during the period early after transplantation prior to the development of any GVL effect. Although the preliminary results are promising,[12,19] better control of the disease with rituximab in this setting remains hypothetical. Kamble *et al*.[26] recently reported that refractory acute GvHD improved in three patients after treatment with rituximab, suggesting a potential role for B cells in the pathogenesis of acute GvHD. Although the results still need to be confirmed in larger trials, this latter report raises the possibility that rituximab used in the conditioning regimen or administered after allogeneic SCT may act to improve patients' outcome via better prophylaxis of severe acute GvHD which was found to adversely affect TRM in our study.

Our study shows that patients with chemoresistant LGL have a poor outcome after RIC allogeneic SCT with a high incidence of TRM, possibly attributable to the high number of previous lines of therapy and the use of the grafts from unrelated donors for one third of these patients. This finding strongly questions the validity of performing an allogeneic SCT procedure using a RIC regimen in patients with chemoresistant disease. These patients would more likely benefit from the administration of investigational therapies aimed at controlling the disease before reconsidering the use of allogeneic SCT. We also report a better outcome when the disease is chemosensitive, with patients in CR or PR having 3-year lymphoma-free survival rates of 66% and 52%, respectively. Although the design of our study prohibits speculation about a better timing of RIC allogeneic SCT in second or subsequent relapse, the potential impact of this issue on disease outcome warrants further examination through appropriate prospective trials. We conclude that RIC allogeneic SCT is a valuable therapeutic option in patients with chemosensitive relapsed LGL even after multiple lines of therapy.

Authors' Contributions

NM, MM, GS, and SV designed the study, analyzed the data and wrote the manuscript; SV collected the data; RP and SV performed the statistical analysis; MM, MA, LA, MB, DB, RT, FG, J-PC, PC, TF, NI, MR, HT, J-PV, MK, J-HB, PB, ED, and BL provided the patients.

Conflict of Interest

The authors reported no potential conflicts of interest.

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