Allogeneic hematopoietic stem cell transplantation in patients with diffuse large B cell lymphoma relapsed after autologous stem cell transplantation: A GITMO study

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Abstract

Patients who relapse after an autologous hematopoietic stem cell transplantation (SCT) have a very poor prognosis. We have retrospectively analyzed diffuse large B cell lymphoma patients who underwent an allo-SCT after an auto-SCT relapse reported in the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) database. From 1995 to 2008, 3449 autologous transplants were reported in the GITMO database. Eight hundred eighty-four patients relapsed or progressed after transplant; 165 patients, 19% of the relapsed patients, were treated with allo-transplant. The stem cell donor was related to the patient in 108 cases. A reduced intensity conditioning regimen was used in 116. After allo-SCT, 72 patients (43%) obtained a complete response and 9 obtained a partial response with an overall response rate of 49%; 84 patients (51%) experienced rapid progression of disease. Ninety-one patients died, 45 due to disease and 46 due to treatment-related mortality. Acute graft-versus-host disease was recorded in 57 patients and a chronic GvHD in 38 patients. With a median follow-up of 24 months (2–144) after allo, overall survival (OS) was 39%, and after a median of 21 months (2–138) after allo, progression-free survival (PFS) was 32%. Multivariate analysis indicated that the only factors affecting OS were status at allo-SCT, and those affecting PFS were status at allo-SCT and stem cell donor. This retrospective analysis shows that about one-fifth of patients with diffuse large B cell lymphoma who experience relapse after autologous transplantation may be treated with allogeneic transplantation. Moreover, the only parameter affecting either OS or PFS was the response status at the time of allo-SCT.

Keywords

Diffuse large B cell lymphomaSalvage therapyAutologous stem cell transplantationAllogeneic stem cell transplantationReduced intensity conditioning regimenGraft versus lymphoma

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Introduction

High-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT) has an established role in the treatment of patients with first relapsed aggressive lymphoma [1–3]. The use of auto-HSCT in the first-line treatment of aggressive lymphoma is still a matter of debate, and its use is restricted to clinical trials. The outcome and prognosis of relapsed or progressed after auto-HSCT in patients is poor, with an overall survival of less than 11% at 1 year [4]. Conventional dose salvage chemotherapy can induce disease remission in a small proportion of patients, but it is not long lasting. A second auto-HSCT is sometimes performed and results are disappointing, but it is most likely to benefit patients in prolonged remission after the initial auto-HSCT [5, 6]. Allogeneic hematopoietic stem cell transplantation (allo-SCT) could be considered a therapeutic option for these high-risk patients. The postulated advantages of an allo-SCT include the use of a tumor-free graft and immune-mediated graft-versus-lymphoma effects [7, 8], but the survival benefit is usually offset by a nonrelapse mortality rate. As seen with other transplant indications,

any reduction in relapse achieved with allo-SCT is offset by mortality attributable to the treatment itself [9–13]. This problem has resulted in the exclusion of older patients and those with comorbidities. Similarly, even in younger patients who have relapsed after an autologous transplant, allogeneic transplantation with myeloablative conditioning has been associated with a prohibitive risk of nonrelapse mortality [14–16]. The development of less intensive but highly immunosuppressive conditioning regimens that rely on possible graft-versus-tumor effects have increased the number of patients who are candidates for allografts [17–19], including those who relapse after auto-HSCT as reported in the recent paper by van Kampen et al [20]. To assess the clinical results of an allo-SCT in diffuse large B cell lymphoma (DLBCL) patients, whose disease has failed a prior autologous transplantation, we analyzed 165 patients with diagnosis of DLBCL whose data were reported to the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) registry.

Patients and methods

We have analyzed the GITMO database serching for DLBCL patients treated with autologous transplant from 1995 to 2008 in 93 Italian transplant units, and we have selected those patients who relapsed after auto-HSCT and treated with allo-SCT. We have studied 165 patients with a diagnosis of DLBCL undergoing allo-SCT, after autologous transplantation relapse, in 48 Italian centers. The analysis was based on the allogeneic transplantation GITMO registry data. The procedures followed were in accordance with the ethical standards of the Istitutional Committee on Human Experimentation and GITMO, as well as with the Declaration of Helsinki. All clinical variables were analyzed at the time of allo-transplant, and all patients fulfilled the minimal essential data for analysis including sex, age, chemosensitivity, disease status at allo-transplant, conditioning regimen, stem cell source, stem cell donor, and follow-up data. Various other data were also collected: therapy performed between auto-HSCT and response to allogeneic transplant, allo-transplant relapse, type of therapy after allo-transplant relapse, response to salvage therapy, causes of death, and acute and chronic graft-versus-host disease. The anti-CD20 antibody (rituximab) was used in association with first-line chemotherapy in all patients diagnosed after 2002 and in association with salvage therapy in patients relapsed after 2002 because from that year, the antibody was licensed for the use in DLBCL by the Italian authorities. The choice of conditioning was decided by the treating physicians who followed the center's protocols. All patients were restaged by using total body computed tomography, and in patients with bone marrow infiltration, biopsy was repeated. Nonrelapse mortality was defined as time to deaths without relapse/recurrence. Donor lymphocyte infusion (DLI) was performed according to the following guidelines: Transplant from an HLA identical sibling: first infusion 5×10^6 CD3/kg, second 1×10^7 CD3/kg, third 5×10^7 CD3/kg, and fourth 1×10^8 CD3/kg. Transplant from unrelated donor: first infusion 5×10^5 CD3/kg, second 1×10^6 CD3/kg, third 5×10^6 CD3/Kg, and fourth 1×10^7 CD3/kg.

Statistical analysis

All patients included in the study were considered for statistical analysis. Overall survival (OS) was calculated from allo-transplantation to death for any cause or last contact, while progression-free survival (PFS) was calculated from allo-transplantation to progression, relapse, and death for any causes or last follow-up. OS and PFS were calculated using the Kaplan–Meier product-limit estimate. Nonrelapse mortality was evaluated with a competing risks analysis. The log rank test was used to assess the significance of differences for each prognostic factor in the univariate analysis. All factors reported in the database were analyzed, and those showing a significant impact, or a trend towards an impact in the univariate analysis ($p < 0.15$), were entered into the multivariate analysis. Multivariate analysis was performed using the Cox proportional hazards regression model, utilizing a stepwise conditional backward method. Data were analyzed using the Statistical Package for Social Science version 13.0 [21], except for the cumulative incidence analyses that were

performed with the NCSS97 [22]. The limit of significance for all the analyses was defined as $p = 0.05$.

Results

Our analysis of the GITMO database from 1995 to 2008 in 93 Italian transplant units indicated that 3449 patients were treated with autologous stem cell transplantation. After a median observation period of 12 months, 293 patients were lost to the follow-up, and 884 patients relapsed or progressed after autologous transplant. One hundred sixty-five (19%) of these 884 patients were then treated with allo-transplant. The last follow-up was in July 2009. Table 1 shows the patients' characteristics. Patients' median age at auto-HSCT was 41 years (15–62), and median age at allo-SCT was 43 years (16–65). One hundred ten patients (67%) responded to any type of salvage therapy used and 55 did not. The disease status at allo-SCT was complete remission (CR) in 53 patients (32%), partial remission (PR) in 38 (23%), and stable disease and progressive disease in 74 patients (45%).

Table 1 Patients' characteristics

Variables	Number, *n* (%)
Patients	165
Median age at allo-SCT	43 (16–65)
Male	90 (55)
Female	75 (45)
Interval from auto-HSCT to allo-SCT in months, median (range)	13 (3–128)
12 or less	82 (49.5)
More than 12	83 (50.5)
Conditioning regimen	
Myeloablative	49 (30)
Reduced intensity	116 (70)
Disease status before allo-HSCT	
Complete remission	55 (33)
Relapsed or persistent disease, chemosensitive	29 (18)
Relapsed or persitent disease, untreated after auto-HSCT	26 (16)
Relapsed or persistent disease chemoresitant	55 (33)
Years of allo-HSCT	
1995–2001	18 (11)
2002–2008	147 (89)
No. of centers reporting	48

Patients, disease, and transplant characteristics

The median interval between auto-HSCT and allo-SCT was 13 months (range 3–128 months). One hundred eight patients (65%) received transplants from an HLA-identical sibling and 57 (35%) from an unrelated donor which were HLA I class locus A and B identical with low resolution and DRB1 (high resolution) 6/6 matched. The conditioning regimen was myeloablative in 49 patients (30%) and nonmyeloablative or with reduced intensity conditioning (RIC) in 116 (70%). The conditioning regimen was reported in 73 RIC patients (19 with TBI, 26 with fludarabin containing regimen, 24 with tyotepa containing regimen, and 4 with busulfan containing regimen), and in 34 myeloablative conditioning therapy patients (11 with TBI, 6 with busulfan containing regimen, and 17 with tyothepa containing regimen). The two groups of patients were not comparable for complete remission status at allo-SCT and chemosensitive disease which was higher in

the reduced intensity conditioning group (Table 2). Graft-versus-host disease (GvHD) prophylaxis was performed according to single institution practice. In particular, it was possible to collect the data in 78 patients, 52 treated with nonmyeloablative conditioning and 26 with myeloablative conditioning. In nonmyeloablative conditioning, 30 patients were treated with cyclosporine and methotrexate; 5 with cyclosporine, methotrexate, and ATG; 5 with cyclosporine; 4 with cyclosporine and mycophenolate; 3 with cyclosporine, mycophenolate, and anti-CD52; and 5 other. In patients with myeloablative regimen, 19 patients were treated with cyclosporine and methotrexate, 3 with cyclosporine, and 4 other. An acute GvHD was registered in 60 patients (36%): grade 1 in 18 patients, grade 2 in 27 patients, grade 3 in 7 patients, grade 4 in 7 patients, and grade 5 in 1 patient. The data in 14 patients were not available. A chronic GvHD was observed in 40 patients (24%): grade 1 in 25 patients and grade 2 in 15 patients. The data in 48 patients were not available. More than two-thirds of allo-SCT (147) were performed in the years between 2002 and 2008 (post rituximab era), whereas the remaining procedures were performed in the previous years (1995–2001). The response to allo-SCT was not evaluable in 55 patients, and they were considered nonresponders; it was evaluable in 110 patients and was completed in 72 patients (65%) and partial in 9 (8%). Considering all patients, the overall response rate was 49%. Twenty-nine patients were nonresponders or presented a rapid progression of disease. Thirty-nine out of 112 (28%) patients, not in complete remission at the time of allo-SCT, achieved a complete remission after allo-transplant.

Table 2

Patients' characteristics according to conditioning regimen (reduced intensity conditioning and myeloablative regimen)

	Myeloablative (49 patients)	**Nonmyeloablative (116 patients)**	***p* value**
Median age in years (range)	38 (16–61)	46 (19–65)	
Male	25 (51%)	65 (56%)	
Female	24 (49%)	51 (44%)	n.s.
Status at allo-HSCT			
Complete remission	10 (21%)	45 (39%)	
Partial remission	9 (18%)	29 (25%)	
Nonresponder	30 (61%)	42 (36%)	0.01
Sensitivity to treatment			
Chemosensitive relapse	25 (51%)	85 (73%)	
Chemorefractory relapse	24 (49%)	31 (27%)	0.003
Donor			
Sibling HLA-identical	32 (65%)	76 (651%)	
Unrelated	17(35%)	40 (35%)	n.s.
Stem cell source			
Bone marrow	9 (18%)	17 (15%)	
Peripheral blood	38 (78%)	96 (82%)	
Both	1 (2%)	1 (1%)	
Cord blood	1 (2%)	2 (2%)	n.s.
Response post allo-HSCT	$n = 30$ patients	$n = 80$ patients	

	Myeloablative (49 patients)	Nonmyeloablative (116 patients)	*p* value
CR	17 (57%)	55 (69%)	
PR	5 (17%)	4 (6%)	
Progressive disease	8 (26%)	21 (25%)	n.s.
Graft-versus-host disease	$n = 30$ patients	$n = 65$ patients	
Acute GVH	20 (67%)	37 (57%)	n.s.
Chronic GVH	10 (33%)	28 (43%)	n.s.
Outcome			
Alive	18 (37%)	56 (48%)	
Dead	31 (63%)	60 (52%)	n.s.

n.s. not significant

Survival outcomes

The median period of observation after allo-SCT for 79 patients who remained alive was 39 months (range 1–144 months): 15 (20%) were alive with lymphoma and 59 (80%) without evidence of lymphoma at last follow-up. Ninety-one patients died: 45 from progressive disease, 33 were due to toxicity other than GvHD, and 13 from acute GvHD. The nonrelapse mortality rate was 28%, and mortality associated with progressive disease was 25%. The cumulative incidence for nonrelapse mortality was significantly associated with alternative donor versus sibling donor (32% versus 19%, $p = 0.05$) (Fig. 1a). Partial response was significantly associated with progressive disease posttransplant versus complete remission posttransplant (30% and 10% versus 9%, $p = 0.03$) (Fig. 1b). Mortality was significantly associated with the disease status at transplant (PR and no response versus CR, $p = 0.001$), chemorefractory disease ($p = 0.05$), alternative donor ($p = 0.03$), and response posttransplant (partial remission and nonresponder versus complete remission, $p < 0.001$). There were no significant differences in OS, regardless of whether relapse was more or less than 1 year post auto-HSCT, with 25 and 49 patients alive and 22 and 69 dead, respectively ($p = 0.9$). A better PFS was observed in patients who relapsed 1 year after auto-HSCT ($p = 0.02$). No differences were observed concerning the conditioning regimen nor when considering the two periods of treatment before and after 2002.

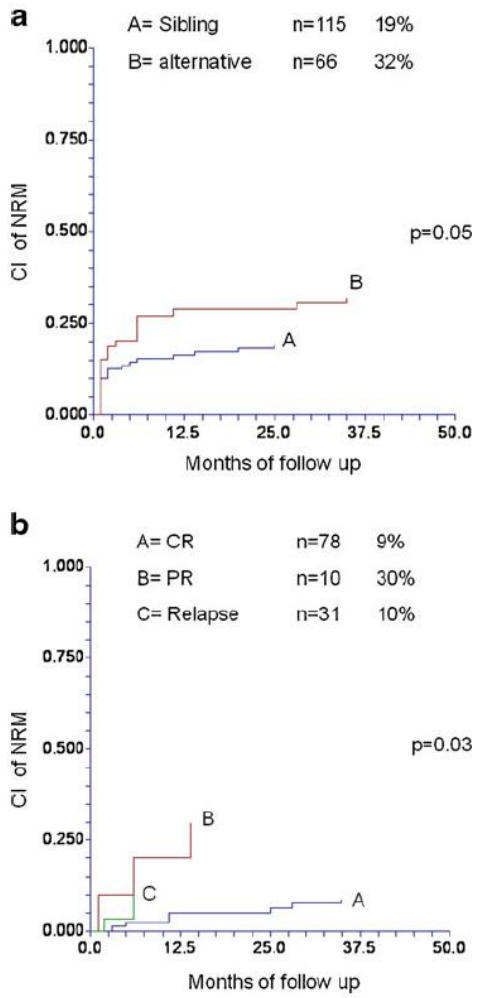

Fig. 1 Treatment related mortality (TRM) or nonrelapse mortality (*NRM*) according to **a** donor and **b** status posttransplant

The Kaplan–Meier estimates of OS after transplantation were 55% at 1 year, 42% at 3 years, and 39% at 5 years with 81, 41, and 22 patients at risk, respectively (Fig. 2) (IC 95%, 36–52). Progression free survival after transplantation was 48% at 1 year, 34% at 3 years, and 31% at 5 years with 81, 41, and 22 patients at risk, respectively (Fig. 3) (IC 95%, 25–43).

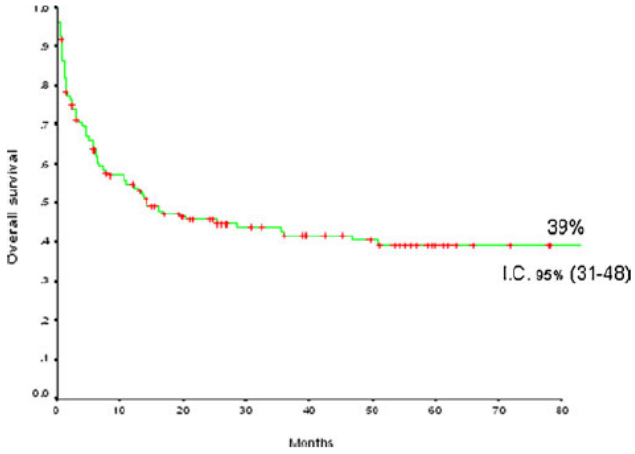

Fig. 2 After a median follow-up of 24 months (range 2-144 months) the Overall Survival was 39% (IC 95% 31-48)

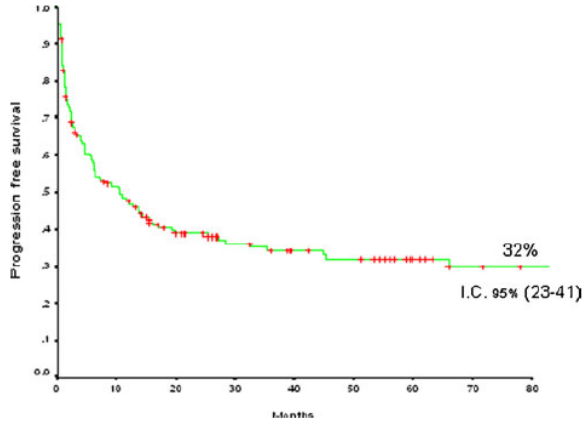

Fig. 3

After a median follow-up of 21 months (range 2-138 months) the Progression Free Survival was 32% (IC 95% 23-41)

According to univariate analysis, the parameters significantly associated with a better OS were CR before patients who underwent allo-SCT, while in complete remission ($p = 0.001$), they were chemosensitive relapse ($p = 0.02$). According to multivariate analysis, the best survival was associated only with disease status at allo-SCT (Fig. 4).

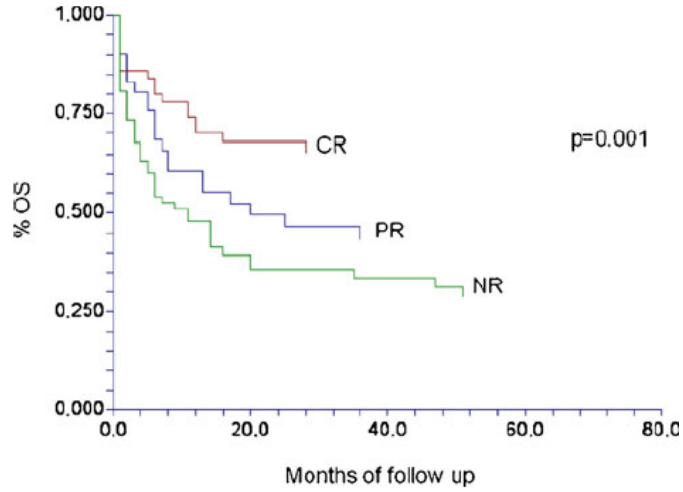

Fig. 4

Overall survival according to status pre allo-transplant (*CR* complete remission, *PR* partial remission, *NR* nonresponders)

According to univariate analysis, the parameters significantly associated with a better PFS were CR before allo-SCT ($p = 0.0008$), chemosensitive relapse ($p = 0.006$), and sibling donor ($p = 0.04$). According to multivariate analysis, the best progression-free survival was associated with disease status at allo-SCT (Fig. 5) and sibling donor.

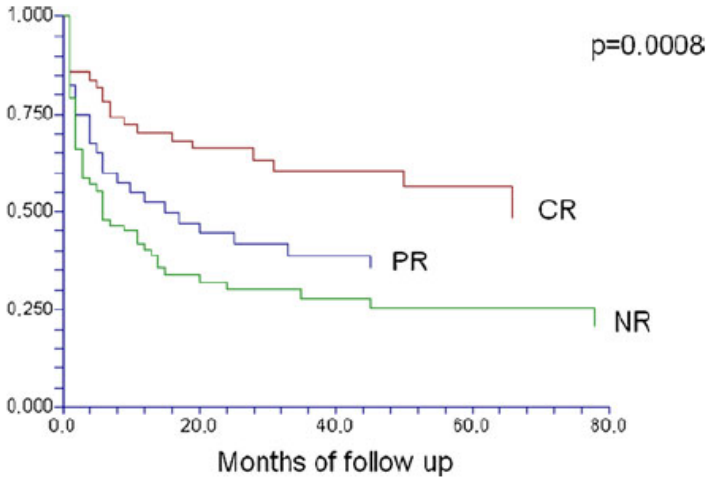

Fig. 5

Progression-free survival according to status pre allo-transplant (*CR* complete remission, *PR* partial remission, *NR* nonresponders)

Therapy for relapse after allo-SCT

One hundred ten patients (67%) relapsed or progressed after allo-SCT and 55 did not. In 66 out of 110 patients (60%), it was not possible to apply any therapy, due to the aggressiveness and rapid progression of the disease. Therapy was possible in 44 patients; donor lymphocyte infusion was performed in 26 patients, a second allo-SCT in 6 patients, and chemoimmunotherapy or radiotherapy in 12 patients. Twenty out of 44 patients treated after allo-SCT relapse obtained a new response, with 12 patients obtaining a new complete response. Six out of 26 patients were treated with DLI (23%), 3 out of 6 (50%) with a second allo-SCT, 3 out of 12 (25%) with chemoimmunotherapy or radiotherapy. Thirteen patients (29.5%) were alive without evidence of disease after a median period of 12 months

Discussion

In this study, we have analyzed the largest group to date of allo-SCT treatment for patients with DLBCL who have relapsed after high-dose therapy and auto-HSCT. This large cohort of patients provides consolidated information that may help clinicians in managing these high-risk patients. Moreover, the GITMO database contains a certain number of obligatory fields concerning the patients.

There are also inherent weaknesses in retrospective registry-based studies. Only patients who undergo transplantation are reported in the registry of a selected population, and in our experience, they represent about 20% of patients relapsed after auto-HSCT. Data submitted from centers may be incomplete despite the requirement for consecutive case reporting and the provision of minimal essential data. Although high-dose chemotherapy with autologous stem cell support is effective, salvage treatment for many patients with relapsed or refractory DLBCL is necessary, and there is a significant number in whom the disease will recur and whose outlook is extremely poor [23]. Patients treated with a second autologous transplant or with conventional therapy after failed autologous transplantation have a very poor prognosis. Vose et al. [4] reviewed the outcomes of 169 patients who had malignant lymphoma and who relapsed after auto-SCT. With a median follow-up of 1 year, 18 (11%) of these 169 patients were alive, off therapy and without evidence of disease

progression. By contrast in this study, 1-, 3-, and 5-year OS were 55%, 42%, and 39%, respectively. Thus, the OS rate of patients included in our study appears to be remarkably higher than that reported for patients treated with conventional therapy after auto-SCT relapse. More recently, in the paper by van Kampen et al. [20], similar results were reported in a larger number of patients.

Allo-SCT is increasingly used because it has the potential advantages of a graft-versus-tumor effect and a tumor-free graft effect. The role of allogeneic transplantation in relapsed DLBCL is currently a field of study with relatively little published data and a lack of consistent findings [6, 14, 16, 24–26]. The toxicity of myeloablative allogeneic transplantation is high, with most groups reporting nonrelapse mortality rates of more than 50%, with the exception of a recent paper by the International Bone Marrow Transplant Registry group that reports a nonrelapse mortality rate of 22% [8, 26–31].

In the present study, nonrelapse mortality was 28%. Approximately a quarter of our patients died from progression of disease after allo-SCT at a mean of 6 months (range 0–45 months). Nonrelapse mortality in our study was mainly affected by alternative donor and lack of response after allo-transplant. In the literature, the reduced intensity conditioning regimen has shown a lower nonrelapse mortality making this a viable option for patients usually excluded from the conventional allo-SCT [32, 33]. There are few published studies on the outcome of reduced intensity conditioning in diffuse large B-cell lymphoma or in aggressive lymphoma [34–39]. For patients with relapsed DLBCL, nonrelapse mortality rates with reduced intensity conditioning allogeneic transplantation, with few exceptions [36, 40], have been surprisingly high (range 25–38%) [34, 41, 42]. In our study, although many features were not comparable between myeloablative or reduced intensity conditioning regimens (see Table 2), no differences were reported in the two groups concerning overall survival and progression-free survival according to univariate analysis. In comparison with low-grade lymphoma treated with allo-SCT, the evidence supporting a graft-versus-tumor effect in aggressive grade lymphoma is less compelling, and while such an effect may exist, its contribution to the prevention of relapse appears to be much less substantial. It is possible that with aggressive-grade lymphomas, the slow-acting graft-versus-lymphoma effect is overridden by the rapidity of growth of the tumor. Many studies report that the status at allo-SCT is one of the most important parameters to predict OS and PFS. In our experience, almost one-third of patients were in CR at the time of allo-SCT. It should be noted that OS and PFS were significantly affected by the CR status at the moment of allo-SCT according to multivariate analysis. Clinical observations of patients undergoing myeloablative and nonmyeloablative allo-SCT suggest that the graft-versus-tumor effects may be important in inducing prolonged remission in patients with lymphoma [15, 43] and that it constitutes one of the rationales for considering allogeneic transplantation. No differences were observed in terms of overall and progression-free survival, the rate of mortality and progression in patients with acute or chronic graft-versus-host disease or those without. This is probably due to the fact that, in our study, only 34% and 23% of patients developed an acute or chronic graft-versus-host disease. Several previous retrospective registry analyses have similarly failed to demonstrate such an effect [44, 45].

Information about outcomes of chemorefractory patients following myeloablative or reduced intensity conditioning allo-transplant is limited. Two studies suggest significantly inferior outcomes of such patients compared to those with chemosensitive relapse [41, 46]. In a recent paper, Sirvent and colleagues [47] concluded that reduced intensity allogeneic transplantation is an attractive option that prolongs survival in high-risk diffuse large B-cell lymphoma patients. In our study, it is clear that patients with chemosensitive relapse show a better overall and progression-free survival in comparison to chemorefractory patients. Nevertheless, it is important to note that overall survival was 27% in chemorefractory patients, showing the existence of an active immunological effect of allogeneic transplantation. Moreover, patients who relapsed after allo-SCT obtained a new response

with immunological therapy (second allo-transplant or DLI), assuming the emergence of graft-versus-lymphoma immune responses.

In summary, it is apparent from the present study that about one-fifth of the patients with DLBCL who experience relapse after autologous transplantation may be treated with allogeneic transplantation. Those who respond to salvage therapy and who have HLA identical siblings have a relatively good 3-year overall and progression-free survival.

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