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Autologous

Autologous Stem Cell Transplantation for Follicular Lymphoma: Favorable Long-Term Survival Irrespective of Pretransplantation Rituximab Exposure

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High-dose chemotherapy supported by autologous stem cell transplantation (HDT/ASCT) has contributed to modify the natural history of follicular lymphoma (FL); however, an overall survival (OS) benefit has been demonstrated at relapse only after a rituximab-free chemotherapy regimen. A total of 655 patients with FL were reported to the Spanish GELTAMO (Grupo Español de Linfomas y Trasplantes de Médula Ósea) registry and underwent first ASCT between 1989 and 2007. A total of 203 patients underwent ASCT in first complete response (CR1), 174 in second complete response (CR2), 28 in third complete response (CR3), 140 in first partial response (PR1), 81 in subsequent PR, and 29 with resistant/refractory disease; 184 patients received rituximab before ASCT. With a median follow-up of 12 years from ASCT, median progression-free survival (PFS) and overall

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survival (OS) were 9.7 and 21.3 years, respectively. Actuarial 12-year PFS and OS were 63% (95% confidence interval [CI], 58%-68%) and 73% (95% CI, 68%-78%), respectively, for patients in CR (with a plateau in the curve beyond 15.9 years), 25% (95% CI, 19%-28%) and 49% (95% CI 42%-56%), respectively, for patients in PR, and 23% (95% CI, 8%-48%) and 28% (95% CI, 9%-45%), respectively, for patients with resistant/refractory disease ($P < .001$). In patients who received rituximab before ASCT, the estimated 9-year PFS and OS from ASCT were 59.5% (95% CI, 51%-67%) and 75% (95% CI, 68%-83%), respectively. Interestingly, for patients who underwent transplantation in CR ≥2 or PR ≥2 who had received rituximab before ASCT (n = 90), 9-year PFS and OS were 61% (95% CI, 51%-73%) and 75% (95% CI, 65%-80%), respectively, with no relapses occurring beyond 5.1 years after ASCT. The cumulative incidence of second malignancies in the global series was 6.7% at 5 years and 12.8% at 10 years. This analysis strongly suggests that ASCT is a potentially curative option for eligible patients with FL. In the setting of relapse, it is of especial interest in pretransplantation rituximab-sensitive patients with FL.

BACKGROUND

Over the past 30 years, high-dose chemotherapy supported by autologous stem cell transplantation (HDT/ASCT) has been frequently used in eligible patients with follicular lymphoma (FL) requiring treatment, and has been explored as part of consolidation therapy in first remission [1-5] and in the relapsed setting [6,7] Along with conventional chemotherapy, radiotherapy, and anti-CD20 immunotherapy, HDT/ASCT has contributed to modifying the natural history of FL [8-10].

Defining the role of HDT/ASCT in FL remains a challenge, in part because the available treatment options are often associated with prolonged survival, and also because many clinical studies have insufficient follow-up or lack statistical power to assess overall survival (OS). Several phase III trials have demonstrated that patients with FL intensified with HDT/ASCT show improved progression-free survival (PFS) compared with those treated with conventional chemotherapy [1-4,6]; however, to date, randomized trials have shown an OS benefit only when HDT/ASCT is performed in second response [6] but not first response [1-5], likely because results have been interpreted prematurely. FL has a long disease course, and most patients receive several lines of therapy, with prolonged survival after progression [11]; thus, demonstration of an OS benefit requires a long observation period and large numbers of patients [12,13].

The addition of rituximab to conventional chemotherapy was a significant development in FL therapy, with phase III randomized trials demonstrating the benefits, including better OS, of first-line rituximab-containing chemotherapy [14-16] Anti-CD20 maintenance therapy prolongs remission and probably survival, and has become a standard of care after first-line therapy [17]. This approach also has been used in the setting of relapse; however, with the available duration of follow-up, there is not still a plateau in the maintenance context [17,18]. Relapses remain common, especially in high-risk patients, and patients tend to become chemorefractory and to achieve less durable and lower-quality responses after subsequent therapies [11]. Moreover, transformation may occur, and many patients ultimately die from the disease [19]. Modern chemoimmunotherapy regimens, such as bendamustine-rituximab [20] used up front in FL and new therapeutic options at relapse [21,22], show excellent results; however, longer follow-up is needed to analyze these data.

The best results for HDT/ASCT have been reported in patients treated in first or second complete remission (CR) [7,23,24]. In rituximab-treated patients, only 1 randomized trial to date has evaluated the role of HDT/ASCT [1,3] in first-line therapy, and the available retrospective studies at first relapse [25,26] might have insufficient follow-up to determine the efficacy of, and best timing for, this treatment approach. Considering that the follow-up time required to demonstrate an OS benefit is beyond the scope of phase III trials conducted to date, large retrospective analyses with long-term follow-up are crucial for assessing the long-term survival of patients with FL who undergo HDT/ASCT.

METHODS

Study Design and Participants

We analyzed 655 patients in the GELTAMO (Grupo Español de Linfomas y Trasplantes de Médula Ósea) registry database who had nontransformed FL and underwent HDT/ASCT between January 1, 1989, and December 31, 2007, at 44 centers in Spain. All data were updated with a cutoff date of July 31, 2014, including reconfirmation of diagnosis, clinical history, biological characteristics, transplantation details, disease status at HDT/ASCT, early toxicity, occurrence of second malignancies, date of progression, and date and cause of death. Regarding histology, patients were classified according to the Working Formulation into follicular small cleaved cell, follicular mixed small cleaved and large cell, or follicular large cell, and according to the Revised European-American Classification of Lymphoid Neoplasms as follicular non-Hodgkin lymphoma grade 1, 2, or 3 [27].

Response, Disease Status, and Surveillance

Patients' disease status was classified according to whether they had achieved their first CR (CR1), second CR (CR2), or third CR (CR3), or their first (PR1) or subsequent (PR ≥2) partial response (PR) to (immuno)-chemotherapy at the time of HDT/ASCT, or whether they had resistant/refractory disease. According to GELTAMO guidelines, CR was defined as the disappearance of all clinical evidence of disease, with normalization of X-rays, computed tomography scans, and laboratory values that had been abnormal before therapy. PR was defined as a ≥50% reduction in measurable disease for at least 1 month. Resistant/refractory disease was defined as lymphoma that progressed during initial combination chemotherapy or a response of less than PR to salvage therapy. From 1999 onward, response criteria used were those recommended internationally at the time of HDT/ASCT [28]. All patients were required to undergo a complete baseline evaluation before HDT/ASCT, including a physical examination, blood count and serum biochemistry determinations, and a whole-body evaluation. Response was evaluated at 3 months after ASCT. Follow-up procedures were performed every 3 months for the first year after transplantation and every 6 to 12 months thereafter.

Statistical Analysis

The primary study endpoint was OS. PFS was defined as the time from HDT/ASCT to disease relapse/progression or death from any cause. OS was analyzed from the time of HDT/ASCT and also from diagnosis to death from any cause. Surviving patients were censored at last follow-up. Nonrelapse mortality was defined as death from any cause in the absence of disease relapse/progression. OS was compared with a sex- and age-matched population obtained from the Spanish Government Civil Registry.

Patient-, disease-, and transplantation-related factors were compared between groups using the chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables. PFS and OS were analysed using the Kaplan–Meier method, and differences were assessed by the log-rank test. Estimations were represented for the median follow-up. All *P* values

were 2-sided and $P < .05$ was considered to indicate statistical significance. Univariate analyses of PFS and OS were conducted for multiple patient-, disease-, and treatment-related factors. Statistically significant variables were included in multivariate analyses, which were performed using the Cox proportional hazards model.

RESULTS

Series Characteristics

Demographic and disease characteristics at the time of diagnosis and treatment- and transplantation-related parameters for all 655 patients according to the decade of transplantation (1989-1999 or 2000-2007) are summarized in Table 1. The median follow-up for survival from HDT/ASCT was 12.0 years (interquartile range [IQR], 8.1-15.5 years), and that from the time of FL diagnosis was 14.2 years (IQR, 10.9-18 years). In the quartile with the longest follow-up, with 103 surviving patients, the median follow-up from HDT/ASCT was 15.5 years, and that from diagnosis was 17.9 years. These values were 14.2 years and 16.3 years for patients who were rituximab-naïve before HDT/ASCT and 9.0 and 11.9 years for patients with previous rituximab exposure.

As first-line therapy, 76% of the patients (460 of 605) received an anthracycline-based regimen. Before HDT/ASCT, 70% of patients received chemotherapy and 30% received chemotherapy plus rituximab. Of 184 patients with previous rituximab exposure, 123 received rituximab as first-line therapy (induction or maintenance) and 103 as part of salvage therapy (induction or maintenance); 42 patients received rituximab in both scenarios. A total of 89 patients underwent ASCT in first response (CR1, n = 67; PR1, n = 22), and 90 patients underwent ASCT in relapse (CR ≥2, n = 67; PR ≥2, n = 23) who had been treated with rituximab before transplantation.

The median time from diagnosis to HDT/ASCT was 1.9 years (IQR, 0.9-3.5); 28% of patients received HDT/ASCT within 1 year after diagnosis. For transplantation, peripheral blood was used as the progenitor cell source in 86% of patients (median number of $CD34^+$ cells infused, 3×10^6/kg; range, 0.2-37.6 $\times$ 10^6/kg). Only 16.5% of the patients received a total body irradiation (TBI)-containing conditioning regimen. The most commonly used conditioning regimen was carmustine, etoposide, cytarabine and melphalan (BEAM; 344 of 653; 53%), followed by carmustine, etoposide, cytarabine and cyclophosphamide (BEAC; 141 of 653; 22%).

A total of 203 patients (31%) underwent HDT/ASCT after achieving CR1; 85 of 199 patients in whom data were available [43%] required multiple lines of chemotherapy to achieve CR. A total of 174 patients (27%) underwent transplantation in CR2, 28 (4%) underwent transplantation in CR3, 140 (21%) underwent transplantation in PR1, 81 (12%) underwent transplantation in PR ≥ 2, and 29 (4%) underwent transplantation with resistant/refractory disease. Post-HDT/ASCT disease status was assessable in 640 patients. Of these, 585 (91.4%) maintained or upgraded to CR, 32 (5%) maintained or upgraded to PR, and 23 (3.6%) progressed or died. The median duration of first response for patients who did not undergo transplantation as part of first-line therapy was 1.4 years (IQR, 0.75-3.1 years).

Survival and prognostic analyses in the global series

In all 655 patients, the median PFS and OS from HDT/ASCT were 9.7 years (95% CI, 7.1-14.3 years) and 21.3 years (95% CI, 17.1 years to not estimable), respectively (Figure 1). Projected 12-year PFS and OS were 49% (95% CI, 44%-55%) and 66% (95% CI, 62%-71%), respectively. Median OS from diagnosis was 22.5 years (95% CI, 20 years to not estimable). Overall, 273 patients (42%) relapsed following HDT/ASCT (median time to relapse, 1.9 years; IQR, 1.0-3.6 years), and 243 (37%) died. Univariate analyses for PFS and OS are summarized in Table 2. Notably, patients who underwent transplantation within the first year after diagnosis of FL had a 10-year PFS of 58% (95% CI, 49%-66%) and 10-year OS of 77% (95% CI, 68%-85%), which was statistically superior to that obtained in patients who underwent transplantation later (Table 2).

In multivariate analysis (Table 3), disease status at HDT/ASCT was the factor most strongly correlated with PFS (HR, 2.16; $P < .001$) and OS (HR, 2.11; $P < .001$). Time from diagnosis to HDT/ASCT less than 1 year also was associated with better PFS ($P = .02$) and OS ($P = .04$).

Response status at HDT/ASCT and survival in the global series

In patients undergoing HDT/ASCT in CR, projected 12-year PFS and OS were 63% (95% CI, 58%-68%) and 73% (95% CI, 68%-78%), respectively, compared with 25% (95% CI, 19%-28%) and 49% (95% CI 42%-56%) for patients in PR, and 23% (95% CI, 8%-48%) and 27% (95% CI, 9%-45%) for patients with resistant/refractory disease.

Patients who underwent HDT/ASCT in CR1 had projected 12-year PFS and OS of 74% (95% CI, 66%-80%) and 78.5% (95% CI, 72%-79%), respectively (Figure 2). In these patients, number of previous lines of therapy (1 [n = 114] or multiple [n = 85]) had no impact on PFS ($P = .30$) or OS ($P = .08$). For the CR1 group, there was a plateau in the PFS and OS curves beyond 15.9 years of follow-up, at 68.5%. For patients who underwent transplantation in CR2/3, estimated 12-year PFS and OS were 51% (95% CI, 43%-58%) and 66% (95% CI, 58%-64%), respectively, with the curves reaching a plateau beyond this time. For patients who underwent transplantation in PR1, projected 12-year PFS and OS were 29% (95% CI, 21%-37%) and 54% (95% CI, 45%-63%), respectively. Respective values were 18% (95% CI, 9%-27%) and 39% (95% CI, 28%-50%) for patients who underwent transplantation in PR ≥2 and 23% (95% CI, 7%-49%) and 28% (95% CI, 10%-46%) for patients who underwent transplantation with resistant/refractory disease (Figure 2). PFS and OS were significantly different between the CR1 and CR2/3 groups ($P < .001$ for both) and also between the CR2/3 and PR1 groups ($P < .001$ for both). Significant differences were found between the PR1 and PR ≥2 groups and between the PR1 and resistant/refractory disease groups for OS ($P = .004$ and .005, respectively), but not for PFS ($P = .07$ and .30, respectively). No significant difference in PFS ($P = .85$) or OS ($P = .38$) was observed between the PR ≥2 and resistant/refractory disease groups. For OS from diagnosis, patients who underwent transplantation in CR1 had an estimated 12-year OS of 78.5% (95% CI, 72%-85%), compared with 72% (95% CI, 66%-78%) for patients who underwent transplantation in CR2/3 ($P = .20$).

A total of 184 patients underwent upfront consolidation after only 1 line of therapy. Of these, 114 underwent transplantation in CR1 and 69 did so in PR1. These patients had a projected 12-year PFS of 61% (95% CI, 57%-66%) and 12-year OS of 73% (95% CI, 68%-78%).

Effect of rituximab before HDT/ASCT on long-term outcome

In patients who received rituximab before HDT/ASCT versus those who did not, the estimated 9-year PFS from HDT/ASCT was 59.5% (95% CI, 51%-67%) versus 47% (95% CI, 42%-52%) ($P < .001$), and estimated 9-year OS was 75% (95%

Table 1
Main Clinical Features at Diagnosis and Treatment Variables of the Entire Series (n = 655) and According to Decade of Transplantation (1989-1999 or 2000-2007)

Characteristic	Entire Series (n = 655)	1989-1999 (n = 350)	2000-2007 (n = 305)	*P* Value*
Age at diagnosis, yr				
Median (range)	47 (18-73)	46 (18-68)	49 (22-73)	.0001
≤46, n/N (%)	332/649 (51)	201/346 (58)	131/303 (43)	.002
>46, n/N (%)	317/649 (49)	145/346 (42)	171/303 (57)	
Sex, n (%)				
Male	330 (50)	166 (47)	164 (54)	.20
Female	325 (50)	184 (53)	141 (46)	
FL histological grade, n/N (%)				
Grade 1	240/556 (43)	106/264 (40)	134/292 (46)	.70
Grade 2	227/556 (40)	121/264 (46)	106/292 (36)	
Grade 3	89/556 (16)	31/264 (12)	50/292 (17%)	
Working Formulation classification, n/N (%)				
Follicular small cleaved cell	244/613 (40)	123/333 (37)	121/280 (43)	.60
Follicular mixed small cleaved and large cell	273/613 (45)	153/333 (46)	120/280 (43)	
Follicular large cell	96/613 (16)	57/333 (17)	39/280 (14)	
ECOG performance status, n/N (%)†				
0-1	509/592 (86)	273/317 (86)	236/275 (86)	1
1-≥2	83/592 (14)	44/317 (14)	39/275 (14)	
Ann Arbor stage, n/N (%)				
I-II	65/653 (10)	29/348 (8)	36/305 (12)	.60
III-IV	588/653 (90)	319/348 (92)	269/305 (86)	
B symptoms, n/N (%)				
Absent	453/639 (71)	244/346 (71)	209/293 (71)	1
Present	186/639 (29)	102/346 (29)	84/293 (29)	
Nodal sites, n/N (%)				
≤4	213/360 (59)	96/179 (54)	117/181 (65)	.01
>4	147/360 (41)	83/179 (56)	64/181 (35)	
Bone marrow involvement, n/N (%)				
Yes	388/608 (64)	212/331 (64)	176/277 (64)	1
No	220/608 (36)	119/331 (36)	101/277 (36)	
Lactate dehydrogenase, n/N (%)				
High	150/559 (27)	71/293 (24)	79/266 (30)	.40
Normal	409/559 (73)	222/293 (76)	187/266 (70)	
Tumor mass, cm, n/N (%)				
<6	201/472 (43)	101/251 (40)	100/221 (45)	.47
≥6	271/472 (57)	150/251 (60)	121/221 (55)	
Hemoglobin level, g/dL, n/N (%)				
≥12	241/314 (77)	110/147 (75)	131/167 (78)	.75
<12	73/314 (23)	37/147 (25)	46/167 (22)	
β_2-microglobulin level, n/N (%)‡				
Low	169/451 (37)	80/197 (41)	89/254 (35)	
High	282/451 (63)	117/197 (59)	165/254 (65)	.40
FLIPI score, n/N (%)				
Low	108/330 (33)	49/160 (31)	59/170 (35)	.70
Intermediate	120/330 (36)	65/160 (41)	56/170 (33)	
High	102/330 (31)	45/160 (28)	55/170 (32)	
FLIPI 2 score, n/N (%)				
Low	69/312 (22)	32/139 (23)	37/173 (21)	.30
Intermediate	118/312 (38)	57/139 (41)	61/173 (36)	
High	125/312 (40)	50/139 (36)	75/173 (43)	
Time from diagnosis to HDT/ASCT, yr, n/N (%)				
≤1	176/638 (28)	105/346 (30)	71/292 (24)	.38
>1	462/638 (72)	241/346 (70)	221/292 (76)	
Disease status at HDT/ASCT, n/N (%)				
CR1	203 (31)	97 (28)	105 (34)	.02
CR2	174 (27)	79 (23)	94 (31)	
CR3	28 (4)	10 (3)	18 (6)	
PR1	140 (21)	95 (27)	45 (15)	
PR ≥2	81 (12)	45 (13)	35 (11)	
Resistant/refractory disease	29 (4)	19 (5)	8 (3)	
Receipt of rituximab before HDT/ASCT, n/N (%)				
Yes	184/620 (30)	5/338 (1)	179/282 (65)	<.0001
No	436/620 (70)	333/338 (99)	103/282 (35)	
TBI-based conditioning regimen, n/N (%)				
Yes	108/654 (17)	93/350 (27%)	15/304 (5%)	.06
No	546/654 (83)	257/350 (73)	289/304 (95)	
Use of PBPCs for ASCT, n/N (%)				
Yes	517/604 (86)	245/322 (76)	272/282 (96)	.15
No	87/604 (14)	77/322 (24)	10/282 (4)	
Use of ex-vivo manipulation, n/N (%)				
No	492/639 (77)	258/339 (76)	234/300 (78)	.06
Positive selection	100/639 (16)	43/339 (13)	4/300 (1)	
Negative selection	47/639 (7)	38/339 (11)	62/300 (21)	

In some categories, the % values may not sum to 100% because of rounding.
BM indicates bone marrow; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; CR, complete response; PR, partial response; ASCT, autologous stem cell transplantation; HDT, high-dose therapy; TBI, total body irradiation; PBPC, peripheral blood progenitor cells.
* Comparison between transplantations performed in 1989-1999 versus 2000-2007.
† Performance status according to the ECOG scale: 0 to 1, low level of functional impairment; 2 to 4, high level of functional impairment.
‡ According to normal values of each laboratory.

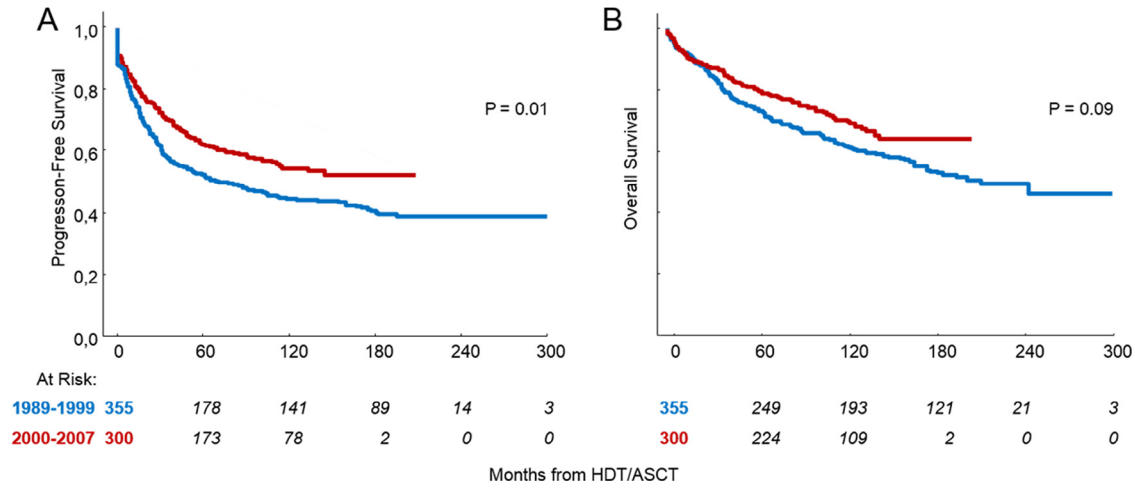

Figure 1. Outcomes in the overall patient population according to the decade of transplantation: 1989-1999 versus 2000-2007. Shown are Kaplan–Meier curves of PFS (A) and OS (B) from the time of HDT/ASCT.

Table 2
Univariate Analysis of Estimated 10-Year PFS and OS Rates Following HDT/ASCT

Parameter		n	10-yr PFS		10-yr OS	
			Rate, %	*P* Value	Rate, %	*P* Value
Age at diagnosis, yr	≤46	332	51	.09	71	.003
	>46	317	47		61	
Sex	Male	330	39	<.001	59	<.001
	Female	325	57		75	
ECOG performance status	0-1	509	49	.57	68	.05
	≥2	83	47		57	
Number of nodal sites	≤4	213	51	.08	69	.01
	>4	147	42		56	
Lactate dehydrogenase	Normal	409	51	.02	69	.004
	High	150	46		58	
FLIPI score	Low	108	53	.14	74	.005
	Intermediate	120	54		69	
	High	102	48		57	
Disease status at HDT/ASCT	CR	405	64	<.001	77	<.001
	PR	221	26		52	
	Refractory	29	23		28	
Received rituximab before HDT/ASCT	Yes	184	58	<.001	73	.02
	No	436	45		62	
Use of PBPCs for ASCT	Yes	517	50	.02	68	.001
	No	87	40		51	
Time from diagnosis to HDT/ASCT, yr	≤1	176	58	.02	77	.04
	>1	462	45		68	
FL histological grade	Grade 1	240	51	.80	67	.047
	Grade 2	227	53		59	
	Grade 3	89	53		53	

ASCT indicates autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HDT, high-dose therapy; OS, overall survival; PBPCs, peripheral blood progenitor cells; PFS, progression-free survival.

Table 3
Multivariate Analysis of PFS and OS Following HDT/ASCT

Variable	PFS		OS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age at diagnosis, yr: >46 versus ≤46	1.18 (0.86-1.5)	.14	1.5 (1.16-1.92)	.002
Sex: male versus female	1.59 (1.37-1.8)	<.001	1.78 (1.38-2.3)	<.001
ECOG performance status: ≥2 versus 0-1	1.09 (0.76-1.42)	.58	1.45 (1.02-2.06)	.04
LDH: high versus normal	1.3 (1.08-1.58)	.09	1.53 (1.16-2.08)	.003
Disease status at HDT/ASCT: refractory versus PR versus CR	2.16 (1.99-2.31)	<.001	2.11 (1.74-2.57)	<.001
Rituximab before HDT/ASCT: no versus yes	1.45 (1.17-1.73)	.008	1.42 (1.02-1.98)	.04
Stem cell source: BM versus PBPCs	1.3 (0 .99-1. 3)	.10	1.67 (1.17-2.37)	.003
Time from diagnosis to HDT/ASCT, yr: >1 versus ≤1	1.45 (1.2-1.6)	.005	1.51 (1.12-2.02)	.007

ASCT indicates autologous stem cell transplantation; HR, hazard ratio; CI, confidence interval; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HDT, high-dose therapy; OS, overall survival; PBPCs, peripheral blood progenitor cells; PFS, progression-free survival.

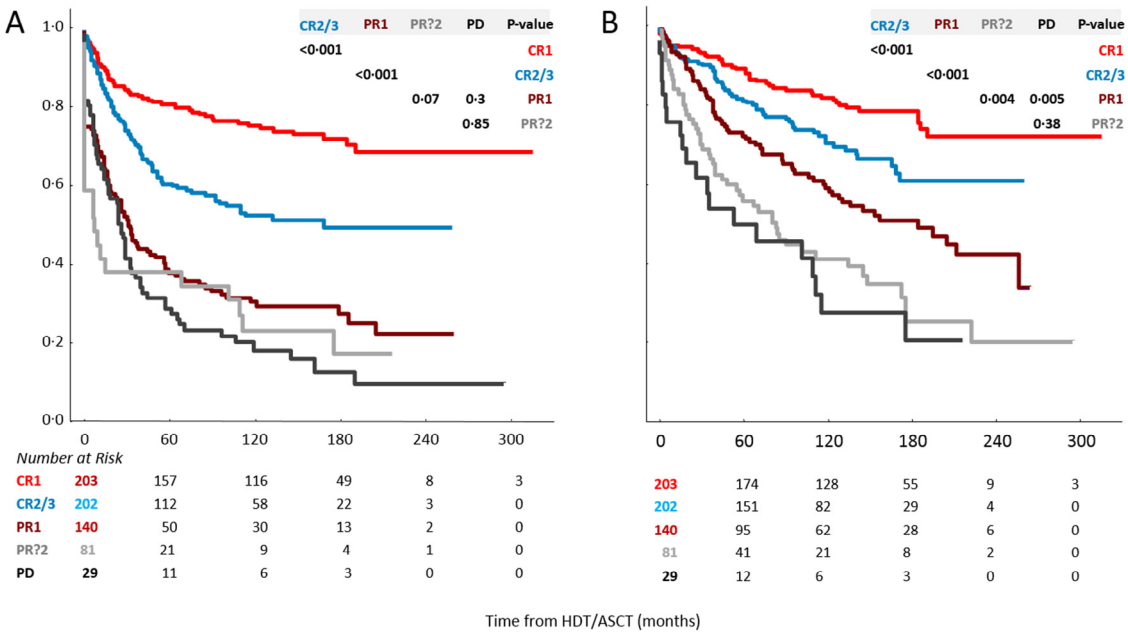

Figure 2. Outcomes in patients according to disease status at transplantation.
Shown are Kaplan–Meier curves of PFS (A) and OS (B) from the time of HDT/ASCT according to disease status at the time of HDT/ASCT. PD, refractory disease.

CI, 68%-83%) versus 65% (95% CI, 60%-69%) ($P = .02$) (Figure 3A and B).

Of special interest is the subgroup of 90 patients who underwent transplantation at relapse after receiving treatment with rituximab (CR ≥2, n = 67 + PR ≥2, n = 23). The median follow-up for survival from HDT/ASCT was 8 years (IQR, 5.1-12.5 years), and that from FL diagnosis was 12.3 years (IQR, 8.9-17.4 years). The median time from diagnosis to HDT/ASCT was 3 years (IQR, 1.9-5.5); 17% of these patients underwent HDT/ASCT within 2 years after diagnosis. Their median duration of first response was 11 months (with a median duration <2 years in 74%). Their estimated 9-year PFS was 61% (95% CI, 51%-73%) and 9-year OS was 75% (95% CI, 65%-80%) (Figure 3 C and D). Overall, 24 patients (26%) relapsed following HDT/ASCT (median time to relapse, 2.4 years; IQR, 1.5-5.6 years), with the last relapse occurring 5.1 years after ASCT, and 21 (23%) died (only 13 [14%] after FL progression).

In patients who underwent transplantation in CR, the benefit of previous rituximab therapy was demonstrated only in the subgroup of patients who underwent transplantation in CR2/3, with an estimated 9-year PFS of 70% (95% CI, 58%-83%) for those with previous rituximab versus 48% (95% CI, 38%-58%) for those without previous rituximab ($P < .001$), and estimated 9-year OS was 87% (95% CI 78%-96%) for those with previous rituximab versus 67% (95% CI 58%-76%) for those without previous rituximab ($P = .009$). However, in the CR1 group, there was no difference in estimated 9-year PFS (78% versus 70%; $P = 0 \cdot 2$), and estimated 9-year OS was 74% versus 85% ($P = .02$) (Figure 4).

Actual versus Expected Survival

OS was significantly shorter for the 655-patient series compared with the age- and sex-matched general Spanish population; estimated 15-year OS was 58% versus 91%, with

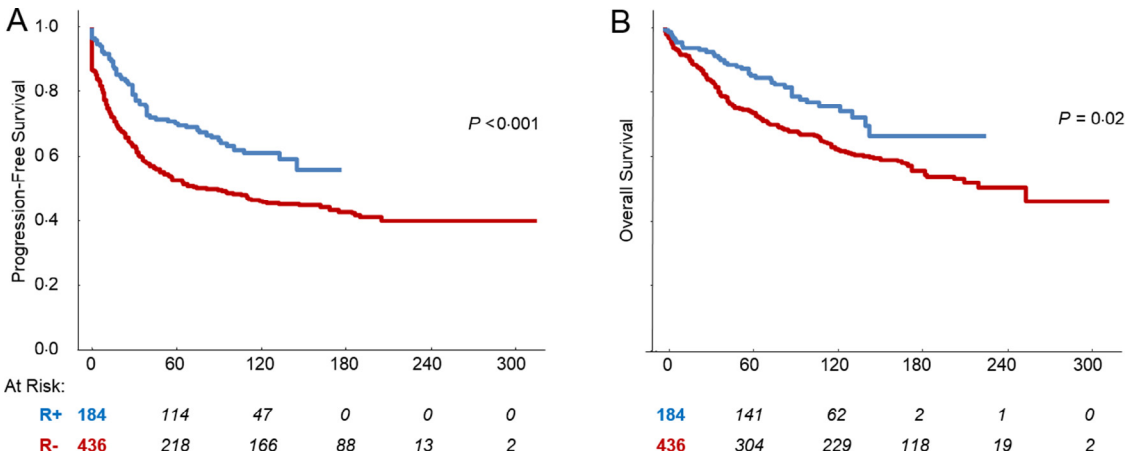

Figure 3. Outcomes in patients according to exposure to rituximab before transplantation. Shown are Kaplan–Meier curves of PFS (A) and OS (B) according to whether patients received rituximab as part of therapy before HDT/ASCT.

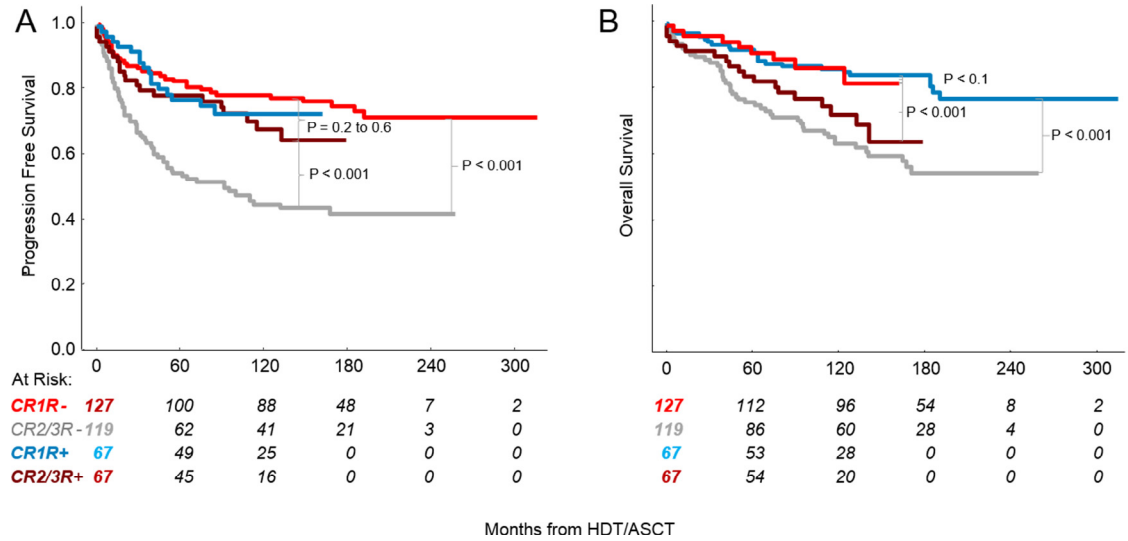

Figure 4. Outcomes in patients who underwent transplantation in CR according to exposure to rituximab before transplantation. Shown are Kaplan–Meier curves of PFS (A) and OS (B) according to whether patients received rituximab as part of therapy before HDT/ASCT and disease status (CR1 versus CR2/3) at the time of HDT/ASCT. R+, patients who had received rituximab before HDT/ASCT. R-, patients who had not received rituximab before HDT/ASCT.

a standardised mortality ratio (SMR) of 7.3 (95% CI, 5.4-9.9; $P < .001$). However, in patients who underwent transplantation in CR1 or CR2/3 who had received rituximab before HDT/ASCT, the difference was less apparent; estimated 15-year OS was 78.5% versus 87% (SMR, 1.7; 95% CI, 1.04-3; $P = .05$) for the CR1 group and 81% versus 92% (SMR, 2.7; 95% CI, 0.9-8.2; $P = .10$) for the CR2/3 group.

Toxic deaths and secondary malignancies

Among all 655 patients, 18 (2.7%) died because of early toxicity within 100 days after HDT/ASCT (6 [7%] of those who received bone marrow versus 12 [2.3%] of those who received peripheral blood progenitor cell transplants; $P = .01$). Nonrelapse mortality at was 4.4% at 1 year, 6.3% at 5 years, and 10% at 10 years. Eighty-three patients (12.75%) developed a total of 85 second malignancies at a median of 5.5 years (IQR, 3.1-9.8) after HDT/ASCT. These malignancies included solid tumors (45 cases [51%], including 8 skin cancers), myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML; 24 cases [43%]), 1 case of acute lymphoblastic leukemia, 1 case of chronic myelogenous leukemia, 1 case of Hodgkin lymphoma, and 2 unspecified malignancies. The cumulative incidence was 6.6% at 5 years and 13% at 10 years (2.5% and 4.9% for solid tumors, and 2.5% and 6.8% for MDS/AML). The median time from HDT/ASCT to the occurrence of MDS/AML was 4.2 years (IQR, 2.4-7.3 years), and that to the occurrence of solid tumors was 7.7 years (IQR, 3.2-9.9 years). Male sex ($P = .02$) and older age ($P = .04$) were associated with an increased number of second malignancies. A response different than CR before ASCT ($P = .06$) was not statistically significant.

DISCUSSION

This retrospective study analyzing survival, toxicity, and prognostic factors in a large series (n = 655) of patients with FL, including a significant number exposed to rituximab before transplantation (n = 184) in the Spanish GELTAMO database who underwent HDT/ASCT was conducted with very lengthy follow-up. A few similar studies have been published with a median follow-up close to ours; however, neither the series from the European Society for Blood and Marrow Transplantation (EBMT) [23] nor that from Rohatiner et al. [7], with only 121 patients in second or subsequent remission, included patients treated with rituximab before HDT/ASCT. Our patients were no younger than those included in other series of FL undergoing HDT/ASCT [3,6,7,25].

In our series, the median PFS and OS from HDT/ASCT were 9.7 years and 21.3 years, respectively. Older age, male sex, poorer performance status, high lactate dehydrogenase concentration at diagnosis, and use of the bone marrow as the stem cell source were associated with poorer OS. Male sex was not previously identified as an adverse factor in historical FL series, but this was demonstrated more recently in rituximab-treated patients [17]. Neither FLIPI 1 nor FLIPI 2 score at diagnosis were good tools for discriminating populations with different outcomes; similarly, other studies did not find poorer outcomes in higher-risk patients [2,3,26].

The most relevant prognostic variable in our series was disease status at HDT/ASCT, a well-established factor [2,3,26,29,30]. Although the strategy of HDT/ASCT consolidation in CR1 has been used frequently in the past [23], it is currently less common owing to the emergence of new treatment options and drugs [31,32]. Our results show that patients who undergo transplantation in CR1, including a high proportion who needed multiple lines of therapy to achieve CR1, had encouraging 12-year PFS and OS from HDT/ASCT of 74% and 78.5%, respectively. Similar encouraging results were seen when OS is calculated from time of diagnosis. Excellent results were obtained in the subgroup of patients who underwent upfront consolidation in either CR1 or PR1, indicating that a significant number of patients can have long-term FL-free survival after just one line of chemotherapy or chemoinmunotherapy.

In addition, the favorable outcome seen in patients who underwent transplantation within the first year after ASCT, with a 10-year PFS of 77% and OS of 58%, indicates that ASCT is of most benefit early in the course of disease, in agreement with recently published results [24].

The apparent plateau in PFS curves after 16 years for patients who underwent transplantation in CR, with 59% of

patients in stable CR, and the fact that the estimated OS for these patients is only slightly worse than that for the age- and sex-matched general population, suggest that substantial numbers of these patients may never relapse and can be considered cured. These findings are consistent with other published findings [2,7,23]. In contrast, the prognosis for patients who undergo transplantation with active disease, including those in PR, is not so promising; our results suggest that some of these patients should be offered new treatment options before considering HDT/ASCT as consolidation therapy.

The French Collaborative Trial in Relapsed Aggressive Lymphoma study [33, 34] has shown that post-HDT/ASCT outcomes in patients with diffuse large B-cell lymphoma who experience relapse after first-line rituximab-containing therapy are significantly inferior compared with those in rituximab-naïve patients, particularly in the context of early relapse. Whether this is true for FL is an open question; however, data from another French study of patients with FL suggest that this is not necessarily the case [25]. In fact, results from our patients, and specifically patients who underwent transplantation in relapse, with no relapses occurring beyond 5.1 years after ASCT, show that previous rituximab therapy does not abrogate the benefit of HDT/ASCT, with PFS and OS benefits in rituximab-exposed patients compared with rituximab-naive patients.

Today, HDT/ASCT is rarely applied in first remission, primarily because randomized studies have not shown an OS benefit for HDT/ASCT at this time point, despite improved PFS, in both the pre-rituximab [2,4,5] and rituximab eras [1,3]. This finding is supported by a recent meta-analysis [35]. However, in our opinion, these studies had insufficient follow-up time to demonstrate an OS advantage for HDT/ASCT, and thus consolidation with HDT/ASCT in the first-line setting should not be dismissed without analyzing updated data from the available studies [12,13]. Incidentally, the excellent results obtained in patients who underwent transplantation in subsequent remissions suggest that approximately one-half, and even more in those treated with rituximab before HDT/ASCT (Figure 3), can achieve very long PFS (median not reached; estimated 9-year PFS, 70%) and possible cure. This positive impact of rituximab sensitivity on HDT/ASCT outcomes has been suggested recently by the Hutchinson Cancer Research Center in 35 patients with relapsed FL [36]. Similar promising results were reported in an analysis from the National Comprehensive Cancer Network with 136 relapsed patients with FL, who achieved a 3-year OS rate of 87% from the time of ASCT.

Although some previous studies have evaluated the role of ASCT in relapsed FL, its role as a first transplantation approach remains unclear. A recent retrospective analysis from the Center for International Blood and Marrow Transplant Research compared long-term outcomes after reduced-intensity allogeneic versus autologous hematopoietic stem cell transplantation in the rituximab era in patients with refractory/relapsed grade 1-2 FL [37] or grade 3 FL [38]. Both strategies demonstrated durable disease control in all grades of FL. In addition, in the first 24 months post-transplantation, HDT/ASCT was associated with improved OS. A similar study from the EBMT did not show significant difference in OS between HDT/ASCT and allogenic stem cell transplantation, although reduced-intensity ASCT was associated with a higher nonrelapse mortality but with a lower relapse rate in relapsed FL [39]. Given the favorable outcomes obtained in our analysis, we suggest HDT/ASCT as a favorable option in relapsed sensitive patients with FL. Allogenic stem cell transplantation could be used in patients who relapse after HDT/ASCT or in patients with refractory FL; nevertheless, randomized prospective clinical trials may be useful to better establish the role of ASCT and allogenic stem cell transplantation in FL.

Our data seem superior to known results from standard chemoimmunotherapy with or without rituximab maintenance [22]. A previous prospective randomized trial of 280 patients with relapsed FL who received HDT/ASCT after salvage chemotherapy [40] that demonstrated a better PFS, but not OS, in patients who received rituximab maintenance after HDT/ASCT, suggesting that the combination of rituximab and HDT/ASCT could be an option in relapsed patients with FL. Unfortunately, we did not address this in our analysis, but it seems to be an attractive option in some high-risk patients with FL.

It is recognized that with the advances in new drugs against FL, this treatment recommendation could have a limited period of validity. Nevertheless, we recognize that these new drugs have side effects that mandate caution with their use, particularly in light of the still short follow-up and the lack of both randomized trials and data on combination regimens [20,21,32,41-43]. On the other hand, we propose HDT/ASCT as an option for countries with limited resources, where the access to maintenance therapy or to rescue treatments based on new drugs can be impossible. In addition, a considerable number of patients could never relapse after a rituximab-free induction plus HDT/ASCT, because this subgroup has a 9-year PFS from the time of HDT/ASCT of nearly 60%.

The occurrence of second malignancies is a concern following HDT/ASCT, with reported incidences varying widely among studies [44,45], and is an argument against this therapy for some experts. A prospective randomized trial of the German Low-Grade Lymphoma Study Group of 440 patients with indolent lymphoma demonstrated an increased risk of secondary hematologic malignancies after HDT/ASCT compared with conventional chemotherapy. However, all patients received a TBI-based conditioning regimen. Moreover, HDT/ASCT significantly improved PFS in this study [46]. However, patients are at increased risk of second malignancy when treated with conventional therapy [20,47,48], which does not differ from that observed in some transplantation series. In our series, the 10-year cumulative incidence of MDS/AML was 6.4%, and that of solid tumors was 4.1%. The substantial number of patients who underwent transplantation in CR and thus did not require treatment after ASCT could explain these good results. Rituximab exposure has been observed to increase secondary solid tumors in some series [45], but not in ours.

Our study has a number of limitations, including the retrospective design, the fact that histology findings were not centrally reviewed, and the use of different response criteria owing to changes over the past 20 years. Nevertheless, the findings are valuable, owing to the very long follow-up and the large number of cases analyzed.

In conclusion, this retrospective analysis on the role of HDT/ASCT in FL has one of the longest follow-ups reported to date. Our findings suggest that a substantial number of patients who undergo transplantation in CR can achieve durable remissions and might be considered cured. Another interesting aspect of ASCT could be its cost- effectiveness, because many patients may not require maintenance therapy or new treatments lines. In patients transplanted in CR1, these results were irrespective of previous rituximab exposure. Interestingly, in

patients who underwent transplantation in second or subsequent responses in the rituximab era—a scenario without randomized studies available—excellent results are demonstrated. Notably, the incidence of second malignancies was not higher than reported in other nontransplantation patient series. Based on these data, we strongly suggest that HDT/ASCT is a beneficial and potentially curative option for intensifying eligible patients with FL who are in CR after conventional chemotherapy or immunochemotherapy, suggesting that this "old tool" continues to be very useful even in the era of rituximab.

CONCLUSION

A considerable number of sensitive patients with FL who underwent HDT/ASCT can reach durable remissions and might be considered cured after a long-term follow-up, irrespective of rituximab exposure. Results obtained in patients who underwent transplantation in second or subsequent responses in the rituximab era—a scenario for which no randomized studies are available—are excellent. Given this strategy's acceptable and well-known security profile, we suggest that this "old tool" continues to be very useful in the era of new drugs.

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