Hematol Oncol Stem Cell Ther xxx (xxxx) xxx

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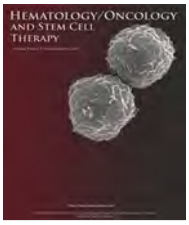

ORIGINAL RESEARCH REPORT

Autologous stem cell transplantation may be curative for patients with follicular lymphoma with early therapy failure without the need for immunotherapy

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https://doi.org/10.1016/j.hemonc.2019.06.001

Please cite this article as: A. Jiménez-Ubieto, C. Grande, D. Caballero et al., Autologous stem cell transplantation may be curative for patients with follicular lymphoma with early therapy failure without the need for immunotherapy, Hematol Oncol Stem Cell Ther, https://doi.org/10.1016/j.hemonc.2019.06.001

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Received 7 November 2018; accepted 23 June 2019

KEYWORDS
Autologous stem cell transplantation;
Early relapse;
Follicular lymphoma;
Survival, chemotherapy

Abstract
Objective/Background: Patients with follicular lymphoma (FL) with early therapy failure (ETF) within 2 years of frontline therapy have poor overall survival (OS). We recently reported the results of autologous stem cell transplantation (ASCT) in patients from the Grupo Español de Linfomas y Trasplantes de Médula Ósea (GELTAMO) registry treated with rituximab prior to ASCT and with ETF after first-line immunochemotherapy, leading to 81% 5-year OS since ASCT. We explored whether ASCT is also an effective option in the pre-rituximab era-that is, in patients treated in induction and rescued only with chemotherapy.
Methods: ETF was defined as relapse/progression within 2 years of starting first-line therapy. We identified two groups: the ETF cohort ($n = 87$) and the non-ETF cohort ($n = 47$ patients receiving ASCT but not experiencing ETF following first-line therapy).
Results: There was a significant difference in 5-year progression-free survival between the ETF and non-ETF cohorts (43% vs. 57%, respectively; $p = .048$). Nevertheless, in patients with ETF with an interval from first relapse after primary treatment to ASCT of <1 year, no differences were observed in 5-year progression-free survival (48% vs. 66%, respectively; $p = .44$) or in 5-year OS (69% vs. 77%, $p = .4$). Patients in the ETF cohort transplanted in complete remission showed a plateau in the OS curves, at 56%, beyond 13.7 years of follow-up.
Conclusion: ASCT may be a curative option for ETF in patients who respond to rescue chemotherapy, without the need for immunotherapy or other therapies, and should be considered as an early consolidation, especially in patients with difficult access to rituximab.

Introduction

Follicular lymphoma (FL) is the most frequent subtype of indolent non-Hodgkin lymphoma. Treatment improvements in the past four decades have contributed to modifying the natural history of FL, with median overall survival (OS) approaching 20 years [1—3]. Nevertheless, FL remains largely incurable, relapses are common, and patients are often chemorefractory and achieve less durable and lower-quality responses after subsequent therapies [4]. Moreover, transformation may occur, and many patients ultimately die from the disease [5,6].

Prior to the approval of rituximab for the treatment of non-Hodgkin lymphoma, combination chemotherapy and prolonged therapy for patients with advanced FL requiring treatment were shown to improve response rates and extend first remission as compared with short-term alkylating agents alone, but with no improvement in OS [7]. 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 [8—10]. Anti-CD20 maintenance therapy prolongs remission and likely survival, and has become a standard of care after first-line therapy [11]. However, for some patients, especially those in underdeveloped countries, access to rituximab is difficult because of its high cost [12].

Several studies have shown that 15—20% of patients with FL do not respond to first-line chemo-/immunochemotherapy (refractoriness) or will experience early therapy failure (ETF), defined as relapse or progression within 2 years of commencing first-line chemo/immunochemotherapy [13—17]. The outcome for this subgroup of high-risk FL patients is much worse than for those responding well to first-line treatment, with reported 5-year OS of approximately 50% versus 90% in the latter [15].

Several retrospective series have shown promising outcomes in relapsed/refractory FL irrespective of previous rituximab use [12—21]. No randomized study has thus far evaluated the role of autologous stem cell transplantation (ASCT) in relapsed FL in the rituximab era; however, in patients naive to rituximab, the randomized European CUP (cancer of unknown primary site) study showed an OS advantage for ASCT over standard chemotherapy in relapsed FL [22]. Nevertheless, there were too few patients in this study who presented relapse within the first 2 years from

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diagnosis, and no information was provided regarding their specific outcome compared with those who experienced a later relapse.

At present, there are no standard therapeutic options for high-risk early failure FL, and considerable effort has been placed on investigating novel therapies in this setting. We recently published the results of ASCT in patients with FL from the Grupo Español de Linfomas y Trasplantes de Médula Ósea (GELTAMO) registry, treated with rituximab prior to transplant and with ETF after first-line therapy [23]. These patients had excellent survival, with 5-year OS since ASCT > 80%. In the present study, we sought to analyze whether ASCT is also an effective option in this high-risk subgroup of FL patients prior to the use of rituximab, that is, in patients treated in induction and rescued only with chemotherapy.

Patients and methods

Study design and participants

The GELTAMO registry database includes 655 patients with non-transformed FL who received ASCT between January 1, 1989 and December 31, 2007, at 44 centers in Spain. Of this total, we identified 255 patients who underwent transplantation in either second complete response (CR2) or second partial response (PR2). Data on duration of response to first-line immunochemotherapy were available for 202 patients; of these, a total of 134 patients (66%), who were transplanted in either CR2 ($n = 94$) or PR2 ($n = 40$), were naive to rituximab prior to ASCT. Therefore, the population for this analysis comprised 134 non-transformed FL patients with known duration of response to first-line therapy (Fig. 1). Regarding histology, patients were classified per 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 non-Hodgkin lymphoma follicular Grade 1, 2, or 3 [24]. In this analysis, ETF was defined as relapse/progression within 2 years of starting first-ine chemotherapy. Patients in the GELTAMO registry who underwent their first ASCT and experienced relapse/progression within 2 years of starting first-line therapy and underwent ASCT following achievement of a CR2 or PR2 comprised the ETF cohort. Outcomes were compared with those patients in the GELTAMO registry who received their first ASCT in either CR2 or PR2, but who did not experience ETF following first-line therapy. All the patients needed treatment at the time of initiation of salvage treatment according to Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria [25].

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

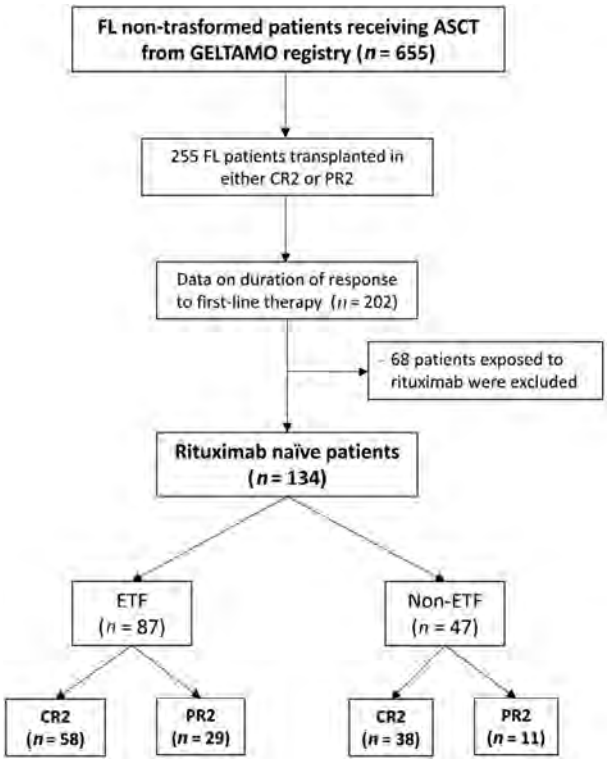

Fig. 1 CONSORT diagram for follicular lymphoma patients in the GELTAMO study. ASCT = autologous stem cell transplantation; CONSORT = Consolidated Standards of Reporting Trials; CR = complete response; ETF = early therapy failure; FL = follicular lymphoma; GELTAMO = Grupo Español de Linfomas y Trasplantes de Médula Ósea; PR = partial response.

Response and disease status

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 prior to therapy; PR was defined as ≥50% reduction in measurable disease for ≥1 month; and 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 high-dose therapy [26]. As the timing of ASCT in relapse/refractory FL is not uniform across transplant centers, we compared outcomes of ETF in FL patients who underwent, or not, an early ASCT consolidation. Early ASCT was defined as transplantation performed within 1 year of ETF. The intent of this analysis was to evaluate the impact of early ASCT in FL patients with ETF.

Statistical analysis

The primary study end point was OS. Progression-free survival (PFS) was defined as the time from ASCT to disease relapse/progression or death from any cause. OS was ana-

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lyzed from the time of ASCT. Surviving patients were censored at last follow-up. Patient-, disease-, and transplantation-related factors were compared between groups using the χ^2 test for categorical variables and the Mann–Whitney *U* test for continuous variables. PFS and OS were analyzed using the Kaplan–Meier method, and differences were assessed using the log-rank test. All *p* values were two-sided, and $p < .05$ was considered statistically significant. 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

Baseline characteristics

Of the 134 patients included in the analysis, 87 experienced ETF. Of these, 58 were transplanted in CR2 and 29 in PR2. The non-ETF cohort comprised 47 patients who achieved CR/PR and progressed more than 2 years after starting first-line therapy. Of these, 36 were transplanted in CR2 and 11 in PR2. The time interval from first relapse after primary treatment to ASCT was 10 (range 4–56) months and 10 (range 4–37) months for the ETF and non-ETF cohorts, respectively ($p = .9$). In the ETF and non-ETF groups, a total of 78% (68/87) and 83% (39/47) of the patients, respectively, received ASCT within the 1st year after treatment failure ($p = .5$). The median follow-up from ASCT for the 134 patients was 13.4 years (range 9–97 months). The median time to progression within first-line therapy was 11 (range 0.1–23) months and 47 (range 25–114) months for patients in the ETF and non-ETF cohorts, respectively ($p < .00001$).

As first-line therapy, patients received either an anthracycline-based (70%; 94/134) or a fludarabine-based (2%; 3/134) regimen. Regarding rescue treatment, of the 106 patients with known data, 50% (53/106) received a cisplatin-based regimen, 21% (22/106) a fludarabine-based regimen, and 29% (31/106) an anthracycline-based regimen. For transplantation, peripheral blood (PB) was used as the progenitor cell source in 79% of patients (median number of $CD34^+$ cells infused 2.7×10^6/kg; range, 0.7–15.4×10^6/kg). A total of 33/134 patients (25%) received a total body irradiation-containing conditioning regimen. The most commonly used conditioning regimen was carmustine, etoposide, cytarabine, and melphalan (BEAM; 46%; 61/134).

Patient/disease characteristics were well balanced between the ETF and non-ETF cohorts. The only differences were in the status according to the Eastern Cooperative Oncology Group (ECOG) scale, with more patients having ECOG ≥ 2 in the non-ETF group; and in the response to frontline chemotherapy, with more patients reaching CR in the non-ETF group (98% vs. 84%, $p = .01$; Table 1). In the ETF cohort, there were no differences between the group who received ASCT within 1 year ($n = 68$) versus > 1 year ($n = 19$) after first relapse, after primary treatment.

Survival analysis and predictors of survival

A significant difference was found for PFS ($p = .048$) between the ETF ($n = 87$) and non-ETF cohorts ($n = 47$), with 5-year PFS rates from the time of ASCT of 43% (95% confidence interval [CI], 33–55%) and 57% (95% CI, 44–71%), respectively (Fig. 2A). Nevertheless, in patients experiencing ETF with an interval from first relapse after primary treatment to ASCT of <1 year ($n = 68$), the 5-year PFS was 48% (95% CI, 36–60%), which was similar to that of the non-ETF cohort ($n = 19$) (5-year PFS: 66%; 95% CI, 46–80%; $p = .44$). No significant difference was found for OS ($p = .4$) between the ETF and non-ETF cohorts, with 5-year OS rates from the time of ASCT of 69% (95% CI, 59–79%) and 77% (95% CI, 65–89%), respectively (Fig. 2B).

In the ETF cohort, multivariate analysis identified that factors associated with a higher risk of mortality (i.e., inferior OS) were male sex (hazard ratio [HR] = 2.46; 95% CI, 1.2–5.03; $p = .01$), older age (HR = 1.27; 95% CI, 1.05–10; $p = .0005$), bone marrow infiltration at diagnosis (HR = 2.24; 95% CI, 1.13–4.4; $p = .02$) and the use of bone marrow as a stem cell source (HR = 5.7; 95% CI, 2.5–13; $p = .00002$). Factors correlating with an inferior PFS were male sex (HR = 2.36; 95% CI, 1.36–4.07; $p = .002$), older age (HR = 1.97; 95% CI, 1.14–3.30; $p = .01$), and the use of bone marrow as a stem cell source (HR = 2.58; 95% CI, 1.37–4.86; $p = .003$).

Response status at ASCT and survival in patients with ETF

Patients with ETF transplanted in CR ($n = 58$) had a better OS (HR = 1.95; 95% CI, 1.06–3.57; $p = .03$) but not a better PFS (HR = 1.42; 95% CI, 0.84–2.42; $p = .1$) than those transplanted in PR ($n = 29$) (Fig. 3). Patients who underwent ASCT in CR ($n = 58$) had a projected 5-year PFS and OS of 47% (95% CI, 33–58%) and 74% (95% CI, 60–83%), respectively. In the latter group, there was a plateau in the OS curves beyond 13.7 years of follow-up, at 56%. Patients who underwent ASCT in PR ($n = 29$) had a projected 5-year PFS and OS of 36% (95% CI, 31–50%) and 57% (95% CI, 48–78%), respectively (Fig. 3).

Causes of death and secondary malignancies

Among all 134 patients, 63 (47%) died: 49 after progression of FL and 14 without presenting progression of the disease. The causes of death of these 14 patients were infection (7 cases), secondary neoplasia (2 cases), cardiotixicity, hemorrhage, graft-versus-host disease (1 case each), and nonspecified nonrelapsed mortality (2 cases). In the ETF and non-ETF cohorts a total of 49% ($n = 43$) and 42% ($n = 20$) ($p = .4$) of patients died. Nineteen patients (14.1%) developed a secondary malignancy (12 cases of solid tumors, including 2 skin cancers and 7 cases of myelodysplastic syndrome/acute myelogenous leukemia) at a median of 9 years after ASCT. Of these 19 patients, 11 have died, and the rest were still alive at last follow-up. In the EFT and non-ETF cohorts, 14 patients (16%) and five patients (10.6%) developed secondary neoplasia ($p = .4$).

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Table 1 Main clinical features at diagnosis and treatment variables of early treatment failure and non-early treatment failure groups.

Characteristics	ETF (n = 140)	Non-ETF (n = 62)	p[a]
Age at diagnosis, y			
Median (range)	47 (25–73)	51 (22–70)	.01
≤46, *n/N* (%)	65/140 (46)	25/62 (40)	
>46, *n/N* (%)	75/140 (64)	37/62 (60)	
Sex, n (%)			
Male	72 (51)	32 (50)	.6
Female	68 (49)	32 (50)	
ECOG performance status, n/N (%)[b]			
0–1	113/132 (86)	59/61 (97)	.02
≥2	19/132 (14)	2/61 (3)	
Ann Arbor stage, n/N (%)			
I–II	20/140 (14)	15/62 (24)	.08
III–IV	120/140 (86)	47/62 (76)	
B symptoms, n/N (%)			
Absent	104/140 (75)	51/62 (82)	.3
Present	36/140 (25)	11/62 (18)	
Nodal sites, n/N (%)			
≤4	50/73 (69)	26/37 (70)	.9
>4	23/73 (31)	11/37 (30)	
Bone marrow involvement, n/N (%)			
Yes	74/133 (56)	29/59 (49)	.4
No	59/133 (44)	30/59 (51)	
Lactate dehydrogenase, n/N (%)			
High	23/115 (20)	12/51 (24)	.6
Normal	92/115 (80)	39/51 (76)	
Tumor mass, cm, n/N (%)			
<6	51/105 (49)	23/44 (52)	.4
≥6	54/105 (51)	21/44 (48)	
Hemoglobin level, g/dL, n/N (%)			
≥12	48/59 (86)	23/29 (79)	.4
<12	8/59 (14)	6/29 (21)	
β2-Microglobulin level, n/N (%)[c]			
Low	29/100 (29)	10/35 (21)	.4
High	71/100 (71)	25/35 (71)	
FLIPI score, n/N (%)			
Intermediate-high	31/56 (55)	17/30 (57)	.9
FLIPI 2 score, n/N (%)			
Intermediate-high	41/57 (72)	23/31 (74)	.9
Response to frontline therapy			
CR2	118/140 (84)	60/62 (97)	.008
PR ≥ 2	17/140 (12)	2/62 (3)	.04

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Table 1 (*continued*)

Characteristics	ETF (n = 140)	Non-ETF (n = 62)	p[a]
Unknown	5/140 (4)	0	
Median lines of therapy to reach first response			
1	111/140 (79)	57/62 (92)	0.02
≥1	29/140 (21)	5/62 (8)	
Time from first relapse after primary treatment to ASCT, y, n/N (%)			
≤1	103/140 (74)	52/62 (84)	.1
>1	37/140 (26)	10/62 (16)	
Disease status at ASCT, n/N (%)			
CR2	95 (68)	50 (81)	.005
PR ≥ 2	45 (32)	12 (19)	
Anthracycline-based induction therapy			
Yes	104/140 (74)	43/62 (69)	.4
No	36/140 (26)	19/62 (31)	
Receipt of rituximab prior to HDT/ASCT, n/N (%)			
Yes	52/140 (37)	16/62 (26)	.1
No	88/140 (63)	46/62 (74)	
TBI-based conditioning regimen, n/N (%)			
Yes	24/140 (17)	10/62 (16)	.9
No	116/140 (83)	52/62 (84)	
Use of PBPCs for ASCT, n/N (%)			
Yes	119/140 (85)	55/62 (89)	.5
No	21/140 (15)	7/62 (11)	
Years of transplant			
1989–1999	73/140 (52)	30/621 (48)	.8
2000–2007	67/140 (48)	32/62 (52)	

Note. In some categories, the % values may not sum to 100% because of rounding. ASCT = autologous stem cell transplantation; CR = complete response; ECOG = Eastern Cooperative Oncology Group; ETF = early therapy failure; FLIPI = Follicular Lymphoma International Prognostic Index; HDT = high-dose therapy; PBPCs = peripheral blood progenitor cells; PR = partial response; TBI = total body irradiation.

[a] Comparison between transplantations performed after an early treatment failure or a non-early treatment failure.

[b] Performance status according to the ECOG scale: 0–1, low level of functional impairment; 2–4, high level of functional impairment.

[c] According to normal values of each laboratory.

Discussion

Patients with FL experiencing ETF following first-line chemotherapy/immunochemotherapy lack effective treatments and ETF has been recently validated as a prognostic marker of poor outcome [15,16,27,28]. Data from the Center for International Blood and Marrow Transplant Research and the National LymphoCare Study on 174 non-ASCT patients and 175 ASCT patients who received a rituximab-based chemotherapy as frontline treatment showed that there were no differences in 5-year OS between the two groups (60% vs. 67%, respectively, p = .16) [29]. However, patients with FL with ETF receiving ASCT soon after treatment failure (≤1 year of ETF, n = 123) had a higher 5-year OS than those without ASCT (73% vs. 60%) [29]. Our previous report from the GELTAMO registry [23], including only patients from the rituximab era, showed no significant difference in PFS (49% vs. 60%, p = .49) or in OS (81% vs. 83%, p = .8) between patients in the ETF or non-ETF cohort. Additionally, patients with early ASCT, performed within 1 year of ETF, showed similar PFS (49% vs. 66%, p = .4) and OS (86% vs. 85%, p = .9) to those in the non-ETF group. Overall, these results suggest that ASCT is an effective treatment option for transplant-eligible patients with high-risk FL who experience ETF in the rituximab era. Nevertheless, it is not known whether this favorable outcome is a consequence of ASCT alone or is the result of a synergistic effect of ASCT plus

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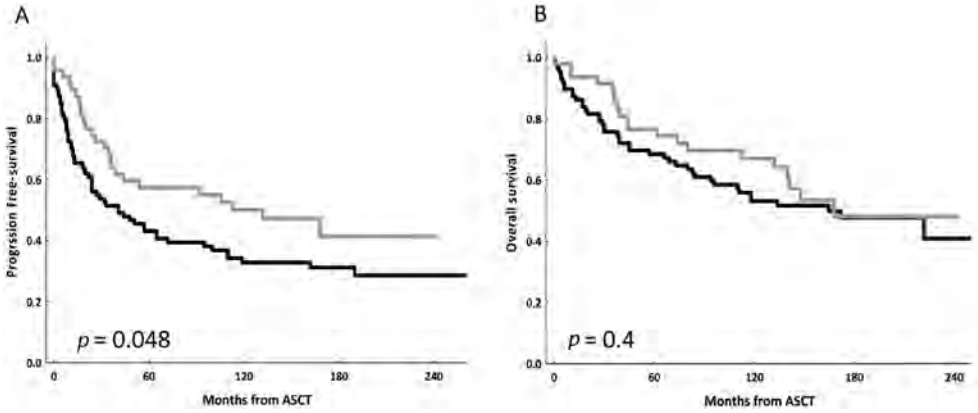

Fig. 2 Kaplan–Meier curves. (A) Progression-free survival and (B) overall survival from the time of autologous stem cell transplantation, according to whether patients had early therapy failure ($n = 87$; black line) or not ($n = 47$; gray line) after first-line therapy. ASCT = autologous stem cell transplantation.

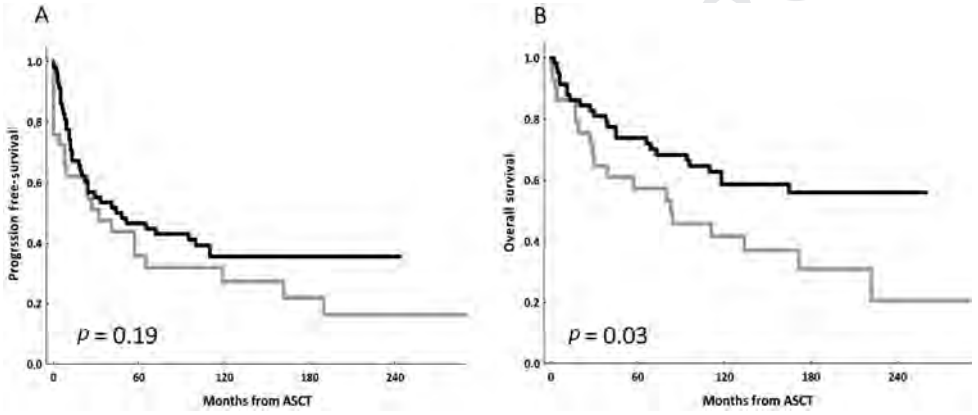

Fig. 3 Kaplan–Meier curves. (A) Progression-free survival and (B) Overall survival from the time of autologous stem cell transplantation (ASCT) in patients presenting early therapy failure according to the status of response at the moment of ASCT: second complete response ($n = 58$, black line) or second partial response ($n = 29$, gray line).

rituximab. In the present study, we demonstrate in a large, long-term follow-up group of rituximab-naive patients that ASCT is also an effective treatment in this setting, reaching a 5-year PFS and OS since the time of ASCT of 43% and 67%, respectively. Interestingly, in patients experiencing ETF with an interval from first relapse after primary treatment to ASCT of <1 year, there were no differences in 5-year PFS (48% vs. 66%, respectively, $p = .44$) between the two cohorts, which was similar to that for patients who received an ASCT with an interval from first relapse after primary treatment to ASCT of <1 year but receiving rituximab prior to transplant (5-year PFS 49%) [23]. A very recent study has reported the results from patients with advanced FL who received frontline treatment within the GLSG1996 or GLSG2000 trials, and who presented with ETF [30]. Those patients who received ASCT ($n = 52$) showed a significant survival benefit with a 5-year second-line PFS versus no transplant patients ($n = 46$) of 51% versus 19% ($p < .0001$) and a 5-year second-line OS of 77% versus 59% ($p = .031$). Of the 52 patients who received ASCT, only 10 had received rituximab prior to ASCT [30]. Moreover, ASCT had a greater impact on improved treatment outcome as compared with second-line rituximab. Similar results have been reported by Le Gouill et al. [20] for patients in the FL2000 study who were in progression after first-line therapy with or without addition of rituximab to chemotherapy and interferon. The authors found a significant difference in 3-year OS (92% vs. 63%, respectively; $p = 0.0003$) between patients receiving ASCT and those who did not. This benefit was relevant irrespective of frontline rituximab exposure. By contrast, Sebban et al. [31] reported a stronger impact of rituximab compared with ASCT in patients in the GELF-86 and GELF-94 trials. Of the 364 patients included in these two studies, 98 had been treated with ASCT, including 33 after rituximab-containing salvage regimen. The 33 patients on combined treatment presented a 5-year survival after relapse >90%, suggesting a possible synergism between the two therapies. Our results on patients treated with the combination of rituximab plus ASCT [23] were somewhat better than those who received ASCT only (5-year PFS and OS of

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Table 2 Clinical practice points.

- Patients with follicular lymphoma (FL) who experience early therapy failure (ETF) within 2 years of frontline therapy have poor overall survival (OS).
- For patients naive to rituximab, the randomized European CUP (cancer of unknown primary site) study showed an OS advantage for ASCT compared with standard chemotherapy in relapsed FL. Nevertheless, there were too few patients who presented relapse within the first 2 years from diagnosis, and no information was available about their specific outcome.
- Our previous study showed that FL patients from the GELTAMO (Grupo Español de Linfomas y Trasplantes de Médula Ósea) with ETF after first-line therapy immunochemotherapy who undergo ASCT have an excellent survival, with 5-year OS since ASCT greater than 80%.
- In the present study, we found that ASCT is also an effective option in ETF FL patients prior to the use of rituximab, leading to a 5-year PFS and OS of 43% and 69%, respectively.
- Patients experiencing ETF with an interval from first relapse after primary treatment to ASCT of < 1 year have similar 5-year PFS to the non-EFT cohort (48% vs. 66%, respectively; $p = .44$). No differences were found when these patients were compared with rituximab-exposed patients who received ASCT with an interval from first relapse after primary treatment to ASCT of <1 year (5-year PFS, 49%).
- These findings suggest that ASCT can be a curative option in ETF FL patients who respond to rescue treatments without the need of rituximab, above all in patients experiencing ETF with an interval from first relapse after primary treatment to ASCT of <1 year. Early ASCT could be a promising option in patients with difficult access to rituximab.

49% vs. 43% and 81% vs. 69%, respectively). However, the differences disappeared when we analyzed exclusively patients experiencing ETF with an interval from first relapse after primary treatment to ASCT of <1 year (5-year PFS 49% vs. 48%, respectively), suggesting that the possible synergistic effect of rituximab plus ASCT is not as relevant if ASCT is offered soon in the course of the disease.

In the present analysis, the time from first relapse after primary treatment to ASCT was 10 months in both the ETF and non-ETF cohorts, with both receiving mostly anthracycline-containing induction regimens. The only relevant difference between the two groups was the ECOG score, with more patients having a performance status according to the ECOG scale $\geq$2 in the non-ETF cohort, and the response status to first-line therapy (significantly better in the non-ETF group). There were no differences in terms of age, status of disease at ASCT, or other already-known prognostic factors in FL. The survival benefit of PB over bone marrow as a stem cell source has been observed in most of the settings, likely because PB is associated with a reduction in the number of platelet transfusions and with the time to platelet and neutrophil recovery [32,33]. Male sex and older age have recently been demonstrated as adverse prognostic factors both in the setting of autologous transplantation [25] and in rituximab-treated patients [11].

Overall, our results suggest that, whereas some patients might benefit from more aggressive therapies, such as allogenic stem cell transplantations, or novel drugs, such as immunomodulatory agents [34], monoclonal antibodies [35], phosphoinositide 3-kinase inhibitors [36], or even the application of bispecific T-cell engagers [37] and chimeric antigen receptor T cells [38], there are a considerable number of patients in this high-risk ETF subgroup that can be cured with ASCT, even in the absence of rituximab (Table 2). This is a hopeful option, especially in patients with difficult access to rituximab, as is the case in many underdeveloped countries.

Our study has several limitations, including its retrospective design, the antiquity of the data, and the absence of a cohort of non-ASCT patients. Nonetheless, we believe the findings are valuable, owing to the very long follow-up and the absence of standard therapeutic options for high-risk early failure FL.

Conclusions

Our results lead us to suggest that ASCT can be a curative option in ETF FL patients who respond to rescue treatments, without the need of rituximab. These results are more favorable when ASCT is performed in patients experiencing ETF with an interval from first relapse after primary treatment to ASCT of <1 year. Thus, early ASCT could be a hopeful option in patients with difficult access to rituximab.

Acknowledgments

The authors acknowledge the patients and their families, all participating members of the GELTAMO study group, Angel Cedillo for administrative support, and Dr. Kenneth McCreath for English editorial assistance, which was funded by the Foundation Research Institute at the Hospital Universitario 12 de Octubre, and complied with Good Publication Practice 3 ethical guidelines (Battisti et al., Ann Intern Med 2015; 163:461–4).

Declaration of Competing Interest

The authors have stated that they have no conflicts of interest.

Authors' contributions

JUA, GC, and LJJ were involved in the study conception and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and manuscript approval. SA, CD, and LG-A were involved in provision of study materials or patients, collection and assembly of data, manuscript writ-

Please cite this article as: A. Jiménez-Ubieto, C. Grande, D. Caballero et al., Autologous stem cell transplantation may be curative for patients with follicular lymphoma with early therapy failure without the need for immunotherapy, Hematol Oncol Stem Cell Ther, https://doi.org/10.1016/j.hemonc.2019.06.001

ing, and manuscript approval. The remaining authors were involved in data analysis and interpretation, and manuscript review and approval.

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