



Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc



ORIGINAL RESEARCH REPORT

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

Ana Jiménez-Ubieto^{a,*}, Carlos Grande^a, Dolores Caballero^b,
Lucrecia Yáñez^c, Silvana Novelli^d, Miguel Teodoro Hernández-García^e,
María Manzanares^f, Reyes Arranz^g, José Javier Ferreiro^h, Sabela Bobilloⁱ,
Santiago Mercadal^j, Andrea Galeo^k, Javier López Jiménez^l,
José M. Moraleda^m, Carlos Vallejoⁿ, Carmen Albo^o, Elena Pérez^p,
Carmen Marrero^q, Laura Magnano^r, Luis Palomera^s, Isidro Jarque^t,
Antonia Rodríguez^a, Leyre Lorza^a, Alejandro Martín^b, Erika Coria^u,
Armando López-Guillermo^r, Antonio Salar^v, Juan José Lahuerta^a,
on behalf of the GELTAMO (Grupo Español de Linfomas y Trasplantes
de Médula Ósea) Cooperative Study Group

^aHospital Universitario, 12 de Octubre, Madrid, Spain

^bHospital Universitario de Salamanca-IBSAL, Salamanca, Spain

^cHospital Universitario Marqués de Valdecilla, Santander, Spain

^dHospital Universitario Sant Pau, Barcelona, Spain

^eHospital Universitario de Canarias, Tenerife, Spain

^fHospital Universitario de Jerez, Jerez, Spain

^gHospital Universitario La Princesa, Madrid, Spain

^hHospital Universitario Donostia-Aránzazu, San Sebastián, Spain

ⁱHospital Universitario Vall de Hebrón, Barcelona, Spain

^jHospital Universitario de Bellvitge, l'Hospitalet de Llobregat, Spain

^kHospital Universitario A Coruña, A Coruña, Spain

^lHospital Universitario Ramón y Cajal, Madrid, Spain

^mHospital Universitario Virgen de la Arrixaca, Murcia, Spain

ⁿHospital Central de Asturias, Asturias, Spain

^oHospital Universitario de Vigo, Vigo, Spain

^pHospital Universitario Morales de Messeguer, Murcia, Spain

^qHospital Universitario Nuestra Señora de La Candelaria, Tenerife, Spain

^rHospital Clinic de Barcelona, Barcelona, Spain

^sHospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

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

1658-3876/© 2019 King Faisal Specialist Hospital & Research Centre. Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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>

39 ^t Hospital Universitario la Fe, Valencia, Spain

40 ^u Hospital Clínico San Carlos, Madrid, Spain

41 ^v Hospital del Mar, Barcelona, Spain

42 Received 7 November 2018; accepted 23 June 2019

43

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

76

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.

© 2019 King Faisal Specialist Hospital & Research Centre. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

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

89 Prior to the approval of rituximab for the treatment of
90 non-Hodgkin lymphoma, combination chemotherapy and
91 prolonged therapy for patients with advanced FL requiring
92 treatment were shown to improve response rates and
93 extend first remission as compared with short-term alkylat-
94 ing agents alone, but with no improvement in OS [7]. The
95 addition of rituximab to conventional chemotherapy was a
96 significant development in FL therapy, with phase III ran-

97 domized trials demonstrating the benefits, including better
98 OS, of first-line rituximab-containing chemotherapy [8–10].
99 Anti-CD20 maintenance therapy prolongs remission and
100 likely survival, and has become a standard of care after
101 first-line therapy [11]. However, for some patients, espe-
102 cially those in underdeveloped countries, access to ritux-
103 imab is difficult because of its high cost [12].

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

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

* Corresponding author at: Hospital Universitario, 12 de Octubre, Avenida de Córdoba s/n, 28041 Madrid, Spain.
E-mail address: anitiju@hotmail.com (A. Jiménez-Ubieto).

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-line 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.

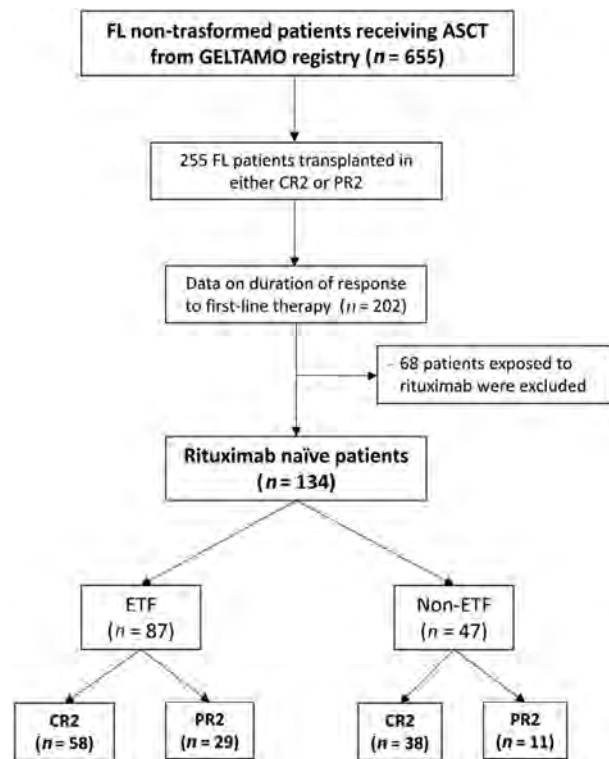


Fig. 1 CONSORT diagram for follicular lymphoma patients in the GELTAMO study. ASCT = autologous stem cell transplantation; CONSORT = Consolidated Standards of Reporting Trials; CR = complete response; ETF = early therapy failure; FL = follicular lymphoma; GELTAMO = Grupo Español de Linfomas y Trasplantes 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 $\geq 50\%$ 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-

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), cardiotoxicity, 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).

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

(continued on next page)

Table 1 (continued)

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

ment 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

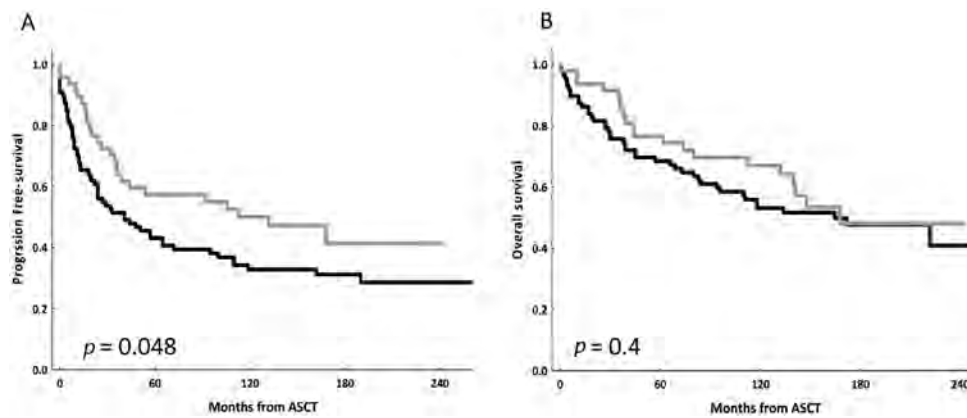


Fig. 2 Kaplan–Meier curves. (A) Progression-free survival and (B) overall survival from the time of autologous stem cell transplantation, according to whether patients had early therapy failure ($n = 87$; black line) or not ($n = 47$; gray line) after first-line therapy. ASCT = autologous stem cell transplantation.

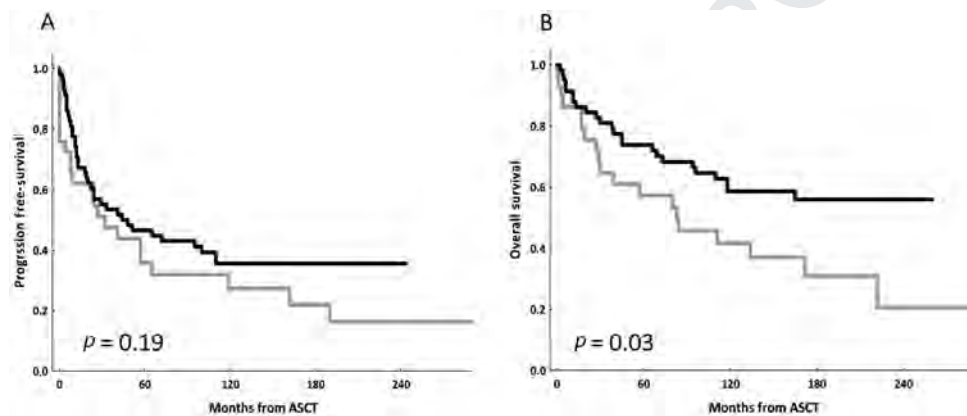


Fig. 3 Kaplan–Meier curves. (A) Progression-free survival and (B) Overall survival from the time of autologous stem cell transplantation (ASCT) in patients presenting early therapy failure according to the status of response at the moment of ASCT: second complete response ($n = 58$, black line) or second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

338 rituximab. In the present study, we demonstrate in a large,
339 long-term follow-up group of rituximab-naïve patients that
340 ASCT is also an effective treatment in this setting, reaching
341 a 5-year PFS and OS since the time of ASCT of 43% and 67%,
342 respectively. Interestingly, in patients experiencing ETF
343 with an interval from first relapse after primary treatment
344 to ASCT of <1 year, there were no differences in 5-year
345 PFS (48% vs. 66%, respectively, $p = .44$) between the two
346 cohorts, which was similar to that for patients who received
347 an ASCT with an interval from first relapse after primary
348 treatment to ASCT of <1 year but receiving rituximab prior
349 to transplant (5-year PFS 49%) [23]. A very recent study
350 has reported the results from patients with advanced FL
351 who received frontline treatment within the GLSG1996 or
352 GLSG2000 trials, and who presented with ETF [30]. Those
353 patients who received ASCT ($n = 52$) showed a significant
354 survival benefit with a 5-year second-line PFS versus no
355 transplant patients ($n = 46$) of 51% versus 19% ($p < .0001$)
356 and a 5-year second-line OS of 77% versus 59% ($p = .031$).
357 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 Guillou 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 inter-
feron. 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 rel-
evant irrespective of frontline rituximab exposure. By con-
trast, 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 com-
bination of rituximab plus ASCT [23] were somewhat better
than those who received ASCT only (5-year PFS and OS of

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 ≥ 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 allogeneic 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-

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

452 References

- 453 [1] Tan D, Horning SJ, Hoppe RT, Levy R, Rosenberg SA, Sigal BM,
454 et al. Improvements in observed and relative survival in
455 follicular grade 1–2 lymphoma during 4 decades: the Stanford
456 University experience. *Blood* 2013;122:981–7.
- 457 [2] Liu Q, Fayad L, Cabanillas F, Hagemester FB, Ayers GD, Hess
458 M, et al. Improvement of overall and failure-free survival in
459 stage IV follicular lymphoma: 25 years of treatment experience
460 at the University of Texas M.D. Anderson Cancer Center. *J Clin
461 Oncol* 2006;24:1582–9.
- 462 [3] Swenson WT, Wooldridge JE, Lynch CF, Forman-Hoffman VL,
463 Chrischilles E, Link BK. Improved survival of follicular lym-
464 phoma patients in the United States. *J Clin Oncol*
465 2005;23:5019–26.
- 466 [4] Johnson PW, Rohatiner AZ, Whelan JS, Price CG, Love S, Lim J,
467 et al. Patterns of survival in patients with recurrent follicular
468 lymphoma: a 20-year study from a single center. *J Clin Oncol*
469 1995;13:140–7.
- 470 [5] Montoto S, Fitzgibbon J. Transformation of indolent B-cell
471 lymphomas. *J Clin Oncol* 2011;29:1827–34.
- 472 [6] Alonso-Álvarez S, Magnano L, Alcoceba M, Andrade-Campos M,
473 Espinosa-Lara N, Rodríguez G, et al. Risk of, and survival
474 following, histological transformation in follicular lymphoma in
475 the rituximab era. A retrospective multicenter study by the
476 Spanish GELTAMO group. *Br J Haematol* 2017;178:699–708.
- 477 [7] Lister TA. High-dose therapy for follicular lymphoma revisited:
478 not if, but when? *J Clin Oncol* 2003;21:3894–6.
- 479 [8] Herold M, Haas A, Srock S, Nesper S, Al-Ali KH, Neubauer A,
480 et al. Rituximab added to first-line mitoxantrone, chlorambucil,
481 and prednisolone chemotherapy followed by interferon
482 maintenance prolongs survival in patients with advanced
483 follicular lymphoma: an East German Study Group Hematology
484 and Oncology Study. *J Clin Oncol* 2017;25:1986–92.
- 485 [9] Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A,
486 Raposo JC, et al. Phase III study of R-CVP compared with
487 cyclophosphamide, vincristine, and prednisone alone in
488 patients with previously untreated advanced follicular lym-
489 phoma. *J Clin Oncol* 2008;26:4579–86.
- 490 [10] Forstpointner R, Dreyling M, Repp R, Hermann S, Hänel A,
491 Metzner B, et al. The addition of rituximab to a combination of
492 fludarabine, cyclophosphamide, mitoxantrone (FCM) signifi-
493 cantly increases the response rate and prolongs survival as
494 compared with FCM alone in patients with relapsed and
495 refractory follicular and mantle cell lymphomas: results of a
496 prospective randomized study of the German Low-Grade
497 Lymphoma Study Group. *Blood* 2004;104:3064–71.
- 498 [11] Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D,
499 Xerri L, et al. Rituximab maintenance for 2 years in patients
500 with high tumour burden follicular lymphoma responding to
501 rituximab plus chemotherapy (PRIMA): a phase 3, randomised
502 controlled trial. *Lancet* 2011;377:42–51.
- 503 [12] Papaioannou D, Rafia R, Rathbone J, Stevenson M, Buckley
504 Woods H, Stevens J. Rituximab for the first-line treatment of
505 stage III–IV follicular lymphoma (review of Technology
506 Appraisal No. 110): a systematic review and economic evalu-
507 ation. *Health Technol Assess* 2012;16:1–253.
- 508 [13] Mozessohn L, Cheung MC, Crump M, Buckstein R, Berinstein N,
509 Imrie K, et al. Chemoimmunotherapy resistant follicular
510 lymphoma: predictors of resistance, association with transfor-
511 mation and prognosis. *Leuk Lymphoma* 2014;55:2502–7.
- 512 [14] Sorigüe M, Mercadal S, Alonso S, Fernández-Álvarez R, García
513 O, Moreno M, et al. Refractoriness to immunochemotherapy in
514 follicular lymphoma: predictive factors and outcome. *Hematol
515 Oncol* 2017;35:520–7.
- [15] Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR,
516 et al. Early relapse of follicular lymphoma after rituximab plus
517 cyclophosphamide, doxorubicin, vincristine, and prednisone
518 defines patients at high risk for death: an analysis from the
519 National LymphoCare Study. *J Clin Oncol* 2015;33:2516–22.
- [16] Murakami S, Kato H, Higuchi Y, Yamamoto K, Yamamoto H,
520 Saito T, et al. Prediction of high risk for death in patients with
521 follicular lymphoma receiving rituximab plus cyclophos-
522 phamide, doxorubicin, vincristine, and prednisolone in first-
523 line chemotherapy. *Ann Hematol* 2016;95:1259–69.
- [17] Jiménez-Ubieto A, Grande C, Caballero D, Yáñez L, Novelli S,
524 Hernández MT, et al. Progression-free survival at 2 years post-
525 autologous transplant: a surrogate end point for overall
526 survival in follicular lymphoma. *Cancer Med* 2017;6:2766–74.
- [18] Jiménez-Ubieto A, Grande C, Caballero D, Yáñez L, Novelli S,
527 Hernández MT, et al. Autologous stem cell transplantation for
528 follicular lymphoma. Favorable long-term survival irrespective
529 of pretransplantation rituximab exposure. *Biol Blood Marrow
530 Transplant* 2017;23:1631–40.
- [19] Vose JM, Bierman PJ, Loberiza FR, Lynch JC, Bociek GR,
531 Weisenburger DD, et al. Long-term outcomes of autologous
532 stem cell transplantation for follicular non-Hodgkin lymphoma:
533 effect of histological grade and Follicular International Prog-
534 nostic Index. *Biol Blood Marrow Transplant* 2008;14:36–42.
- [20] Le Goull S, De Guibert S, Planche L, Brice P, Dupuis J, Cartron
535 G, et al. Impact of the use of autologous stem cell transplan-
536 tation at first relapse both in naive and previously rituximab
537 exposed follicular lymphoma patients treated in the GELA/
538 GOELAMS FL2000 study. *Haematologica* 2011;96:1128–35.
- [21] Evens AM, Vanderplas A, LaCasce AS, Crosby AL, Nademanee
539 AP, Kaminski MS, et al. Stem cell transplantation for follicular
540 lymphoma relapsed/refractory after prior rituximab: a com-
541 prehensive analysis from the NCCN lymphoma outcomes
542 project. *Cancer* 2013;119:3662–71.
- [22] Schouten HC, Qian W, Kvaloy S, Porcellini A, Hagberg H,
543 Johnsen HE, et al. High-dose therapy improves progression-
544 free survival and survival in relapsed follicular non-Hodgkin's
545 lymphoma: results from the randomized European CUP trial. *J
546 Clin Oncol* 2003;21:3918–27.
- [23] Jiménez-Ubieto A, Grande C, Caballero D, Yáñez L, Novelli S,
547 Hernández-García MT, et al. Autologous stem cell transplan-
548 tation may be curative for patients with follicular lymphoma
549 with early therapy failure who reach complete response after
550 rescue treatment. *Hematol Oncol* 2018;36:765–72.
- [24] Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML,
551 et al. Lymphoma classification proposal: clarification. *Blood*
552 1995;85:857–60.
- [25] Sebban C, Mounier N, Brousse N, Belanger C, Brice P, Haioun C,
553 et al. Standard chemotherapy with interferon compared with
554 CHOP followed by high-dose therapy with autologous stem cell
555 transplantation in untreated patients with advanced follicular
556 lymphoma: the GELF-94 randomized study from the Groupe
557 d'Etude des Lymphomes de l'Adulte (GELA). *Blood*
558 2006;108:2540–4.
- [26] Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors
559 JM, et al. Report of an international workshop to standardize
560 response criteria for non-Hodgkin's lymphomas. NCI Sponsored
561 International Working Group. *J Clin Oncol* 1999;17:1244.
- [27] Maurer MJ, Bachy E, Ghesquieres H, Ansell SM, Nowakowski GS,
562 Thompson CA, et al. Early event status informs subsequent
563 outcome in newly diagnosed follicular lymphoma. *Am J
564 Hematol* 2016;91:1096–101.
- [28] Jurinovic V, Kridel R, Staiger AM, Szczepanowski M, Horn H,
565 Dreyling MH, et al. Clinicogenetic risk models predict early
566 progression of follicular lymphoma after first-line
567 immunochemotherapy. *Blood* 2016;128:1112–220.

- 582 [29] Casulo C, Friedberg JW, Ahn KW, Flowers C, DiGilio A, Smith
583 SM, et al. Autologous transplantation in follicular lymphoma
584 with early therapy failure: a National LymphoCare Study and
585 Center for International Blood and Marrow Transplant Research
586 analysis. *Biol Blood Marrow Transplant* 2018;24:1163–71.
- 587 [30] Jurinovic V, Metzner B, Pfreundschuh M, Chmitz N, Wandt H,
588 Keller U, et al. Autologous stem cell transplantation for
589 patients with early progression of follicular lymphoma: a
590 follow-up study of 2 randomized trials from the German Low
591 Grade Lymphoma Study Group. *Biol Blood Marrow Transplant*
592 2018;24:1172–9.
- 593 [31] Sebban C, Brice P, Delarue R, Haioun C, Souleau B, Mounier N,
594 et al. Impact of rituximab and/or high-dose therapy with
595 autotransplant at time of relapse in patients with follicular
596 lymphoma: a GELA study. *J Clin Oncol* 2008;26:3614–20.
- 597 [32] Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA,
598 Ferrant A, et al. Randomised trial of filgrastim-mobilised
599 peripheral blood progenitor cell transplantation versus autol-
600 ogous bone-marrow transplantation in lymphoma patients.
601 *Lancet* 1996;347:353–7.
- 602 [33] Kottaridis PD, Peggs K, Schmitz N, Dreger P, Boogaerts MA,
603 Ferrant A, et al. Survival and freedom from progression in
604 autotransplant lymphoma patients is independent of stem cell
605 source: further follow-up from the original randomised study
606 to assess engraftment. *Leuk Lymphoma* 2002;43:531–6.
- 607 [34] Fowler NH, Davis RE, Rawal S, Nastoupil L, Hagemester FB,
608 McLaughlin P, et al. Safety and activity of lenalidomide and
rituximab in untreated indolent lymphoma: an open-label,
609 phase 2 trial. *Lancet Oncol* 2014;15:1311–8.
- [35] Sehn LH, Chua N, Mayer J, Dueck G, Trněný M, Bouabdallah K,
611 et al. Obinutuzumab plus bendamustine versus bendamustine
612 monotherapy in patients with rituximab-refractory indolent
613 non-Hodgkin lymphoma (GADOLIN): a randomised, controlled,
614 open-label, multicenter, phase 3 trial. *Lancet Oncol*
615 2016;17:1081–93.
- [36] Gopal AK, Kahl BS, Flowers CR, Martin P, Ansell SM, Abella-
617 Dominicus E, et al. Idelalisib is effective in patients with high-
618 risk follicular lymphoma and early relapse after initial
619 chemoimmunotherapy. *Blood* 2017;129:3037–9.
- [37] Goebeler ME, Knop S, Viardot A, Kufer P, Topp MS, Einsele H,
621 et al. Bispecific T-Cell Engager (BiTE) antibody construct
622 blinatumomab for the treatment of patients with relapsed/
623 refractory non-Hodgkin lymphoma: final results from a phase I
624 study. *J Clin Oncol* 2016;34:1104–11.
- [38] Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP,
626 Carpenter RO, Stetler-Stevenson M, et al. Chemotherapy-
627 refractory diffuse large B-cell lymphoma and indolent B-cell
628 malignancies can be effectively treated with autologous T cells
629 expressing an anti-CD19 chimeric antigen receptor. *J Clin*
630 *Oncol* 2015;33:540–9.
- 631
632
633