Autologous stem-cell transplantation as consolidation of first-line chemotherapy in patients with peripheral T-cell lymphoma: a multicenter GELTAMO/FIL study

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Received: July 21, 2021.
Accepted: January 28, 2022.
Prepublished: March 24, 2022.

https://doi.org/10.3324/haematol.2021.279426

Abstract

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of rare lymphoid malignancies that mostly have poor prognoses with currently available treatments. Upfront consolidation with autologous stem cell transplantation (ASCT) is frequently carried out, but its efficacy has never been investigated in randomized trials. We designed a multicenter, international, retrospective study with the main objective of comparing progression-free survival and overall survival of patients with PTCL who underwent ASCT in complete remission (CR) after first-line chemotherapy with a control group who did not undergo ASCT. From the initial population of 286 registered patients, 174 patients with PTCL other than anaplastic large cell lymphoma, ALK-positive, deemed fit for ASCT at the time of diagnosis, and who were in CR or

uncertain CR after induction therapy (CR1) were included in our analysis. one hundred and three patients underwent ASCT, whereas 71 did not, in most cases (n=53) because the physician decided against it. With a median follow-up of 65.5 months, progression-free survival was significantly better in the transplanted patients than in the non-transplanted group: 63% *versus* 48% at 5 years (*P*=0.042). Overall survival was significantly longer for ASCT patients in the subgroup with advanced stage at diagnosis (5-year overall survival: 70% *vs*. 50%, *P*=0.028). In the multivariate analysis, first-line ASCT was associated with significantly prolonged progression-free survival (HR=0.57, 95% CI: 0.35-0.93) and overall survival (HR=0.57, 95% CI: 0.33-0.99). In conclusion, our study supports the use of ASCT as a consolidation strategy for patients with PTCL in CR1. These results should be confirmed in a prospective randomized study.

Introduction

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of rare lymphoid malignancies. With the exception of some primarily cutaneous and leukemic forms, PTCL are aggressive in nature, with rapid disease progression and poor response to treatment.[1] Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), or variants of it, has been the most commonly used regimen for treating nodal PTCL.[2] However, except for anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), prognosis when using this approach remains poor, with 5-year overall survival (OS) rates of around 30% for the remaining PTCL subtypes.[3]

These poor outcomes have prompted many centers to include autologous stem-cell transplantation (ASCT) as part of the first-line treatment of patients with PTCL. This strategy has been evaluated in prospective studies suggesting more favorable outcomes,[4–8] but randomized trials are lacking. In addition, several large retrospective studies have yielded conflicting results,[1,9] so the precise role of ASCT for PTCL remains largely unknown in front-line settings.

Given this background, we designed a large multicenter and international retrospective study with the main objective of analyzing the outcomes of patients with PTCL other than ALK-positive ALCL, who underwent ASCT in complete remission (CR) after first-line chemotherapy, compared with a control group who did not undergo ASCT as part of their first-line treatment (Table 1).

Methods

Patients and study design

This is an international, multicenter, retrospective study designed by the Spanish and Italian lymphoma groups, Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea (GELTAMO) and Fondazione Italiana Linfomi (FIL), performed in accordance with the Declaration of Helsinki and approved in Spain by the national authorities and the institutional ethics committee of Hospital Universitario de Salamanca, and in Italy by the relevant ethics committees and regulatory authorities. Eligibility criteria were: (i) aged 18 to 65 years at diagnosis; (ii) histological diagnosis of PTCL between 2001 and 2011 from the following subtypes:[10] PTCL, not otherwise specified (NOS); angioimmunoblastic T-cell lymphoma; ALCL, ALK-positive; ALCL, ALK-negative; extranodal NK/T-cell lymphoma, nasal type (non-localized cases); enteropathy-associated T-cell lymphoma; hepatosplenic T-cell lymphoma; primary cutaneous γδ T-cell lymphoma; and primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma; (iii) patients deemed fit for ASCT at the time of diagnosis; and (iv) documented partial response (PR), or unconfirmed CR (CRu), or CR after anthracycline-based first-line treatment. Patients who experienced progressive disease within 3 months of the initiation of the last cycle of first-line chemotherapy were not considered to be responders.

Participating centers were required to identify eligible patients from local databases. In each center, all records of patients diagnosed in the designated period were reviewed, and all eligible patients were registered. Data were retrospectively collected from the medical records of all centers. The response to first-line treatment recorded in the study was the response indicated in the medical records according to the clinical judgment of the treating physician, provided that it was supported, at least, by the findings of an imaging study.

Study objectives and statistical analysis

The primary objective was to assess survival in patients with PTCL different from ALCL, ALK-positive who underwent ASCT in CR/CRu after first-line therapy, and compare them with a control non-transplanted group. Secondary objectives were to assess the influence on survival of other prognostic factors, and to assess survival in patients undergoing ASCT in PR after first-line therapy. With respect to the cohort of patients with ALK-positive ALCL (n=41), only six patients underwent ASCT after first-line treatment, two in PR and four in CR. Given the very low number of transplanted patients in this cohort, no worthwhile statistical analysis could be carried out.

A landmark analysis was performed in which time zero was defined as the date of the response assessment after

first-line treatment. The χ^2, Fisher exact or Mann-Whitney test was used for statistical comparison of the ASCT and non-ASCT groups. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Progression-free survival (PFS) was calculated from the date of response assessment after first-line treatment until the date of relapse, progression, or death from any cause. OS was calculated from the date of response assessment after first-line treatment to the date of death or of last follow-up. Multivariate Cox analyses were undertaken to investigate factors that could be prognostic for survival. We tested all factors included in Table 2 in the multivariate regression model, eliminating non-significant terms by backward selection. Age was tested as a dichotomous variable (≤60 *vs*. >60 years, based on the International Prognostic Index [IPI] and Prognostic Index for T-cell lymphoma [PIT] indices). Analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/), and IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA).

Results

Patients' characteristics

Figure 1 shows the study flowchart. From the initial population of 286 registered patients, the 174 patients who were in CR/CRu after induction therapy were included in the primary analysis. The other 112 patients were excluded due to absence of CR/CRu after induction (60 patients; PR, n=53; response to first-line not documented, n=7), presence of ALK-positive ALCL histology (41 patients), relapse within 3 months of the initiation of the last cycle of first-line treatment (7 patients), or for not meeting other inclusion criteria (4 patients). One hundred and three patients underwent ASCT, whereas 71 patients did not undergo transplantation, in most cases because the physician decided against it up-front (n=53). Other reasons why patients did not receive a transplant were patients' condition (n=9), patients' refusal (n=7), pregnancy (n=1) and early relapse (n=1). In these 18 cases, the decision not to proceed to transplant was not taken at the beginning of first-line treatment but well into the treatment or at the end of it. The use of up-front ASCT did not change over time. From the overall series, 58 and 116 patients were diagnosed between 2001-2006 and 2007-2011, respectively, and 34 (58.6%) and 69 (59.5%) patients from the two groups, respectively, underwent ASCT (*P*=0.913).

The patients' characteristics are summarized in Table 1. The median age of patients in the non-transplanted group was older than that in the transplanted group (54 *vs*. 50 years; *P*=0.037), and a higher proportion of the non-transplanted patients were older than 60 years compared with the transplanted patients. On the other hand, a significantly higher proportion of patients in the transplant group had adverse prognostic factors, such as advanced stage or increased lactate dehydrogenase (LDH) level. Approximately 90% of patients in both groups had a nodal PTCL. The proportion of patients with angioimmunoblastic T-cell lymphoma was higher in the transplant group, whereas ALCL was a more frequent diagnosis in the non-ASCT group, although these differences were not statistically significant.

The majority of patients in both groups received CHOP, CHOEP or similar as an induction regimen, although a higher proportion of patients in the transplant group received a CHOP-like scheme that was alternated with other regimens, as shown in Table 1. There were no significant differences in the time between the last cycle of first-line regimen and the evaluation of response between the transplanted and the non-transplanted groups (median of 31.5 days [interquartile range, 22.0-53.0] *vs*. 33.5 days [interquartile range, 26.2-49.5, *P*=0.782]). Radiotherapy was much more frequently administered in the non-transplant group; this was planned at diagnosis in most cases (16 out of 19) because the patients had limited-stage disease.

Survival analysis

With a median follow-up of 65.5 months (range, 4.1-176.7

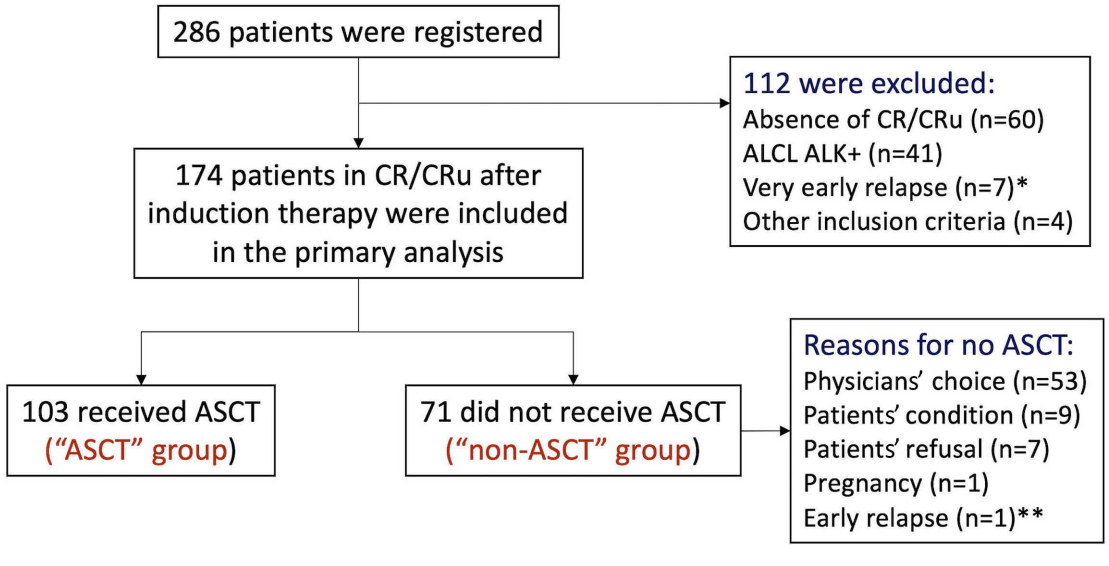

Figure 1. Study flowchart. *Relapse within 3 months of the initiation of the last cycle of first-line treatment. **Relapse beyond 3 months of the initiation of the last cycle of first-line treatment. ALCL: anaplastic large cell lymphoma; ASCT: autologous stem-cell transplantation; CR: complete remission; CRu: unconfirmed complete remission.

Table 1. Patients' characteristics at diagnosis and first-line treatment.

Characteristic	Missing, N	ASCT, N (%)	Non-ASCT, N (%)	*P*
Total number of evaluable patients		103	71	
Male sex	0	62 (60.2)	42 (59.2)	0.507
Age, years, median (range) Older than 60	0	50 (18-65) 12 (11.7)	54 (19-65) 19 (26.8)	0.037 0.010
Histological diagnosis Peripheral T-cell lymphoma, NOS Angioimmunoblastic T-cell lymphoma Anaplastic large cell lymphoma, ALK-negative Enteropathy-associated T-cell lymphoma Hepatosplenic T-cell lymphoma Extranodal NK/T-cell lymphoma, nasal type Primary cutaneous γδ T-cell lymphoma	0	 41 (39.8) 31 (30.1) 19 (18.4) 5 (4.9) 4 (3.9) 2 (1.9) 1 (1.0)	 26 (36.6) 17 (23.9) 19 (26.8) 4 (5.6) 1 (1.4) 4 (5.6) 0	0.336
ECOG performance status 2-4	3	20 (19.6)	7 (10.1)	0.071
Ann-Arbor stage III-IV	1	86 (84.3)	36 (50.7)	<0.001
Lactate dehydrogenase increased	12	54 (55.1)	22 (34.4)	0.007
Bone marrow infiltration	2	33 (32.4)	15 (21.4)	0.080
International Prognostic Index 0-1 2-3 4-5	9	 40 (40.8) 48 (49.0) 10 (10.2)	 39 (58.2) 22 (32.8) 6 (9.0)	0.081
Prognostic Index for T-cell Lymphoma 0-1 2 3-4	5	 66 (64.7) 25 (24.5) 11 (10.8)	 53 (79.1) 7 (10.4) 7 (10.4)	0.067
First-line treatment CHOP or CHOP-like CHOEP or CHOEP-like MACOP-B or VACOP-B CHOP-like alternating with others Others	0	 68 (66.0) 11 (10.7) 4 (3.9) 14[a] (13.6) 6[c] (5.8)	 58 (81.7) 5 (7.0) 3 (4.2) 4[b] (5.6) 1[d] (1.4)	0.155
Radiotherapy as part of first-line treatment	0	3 (2.9)	19 (26.8)	<0.001

[a]ESHAP (n=6), Hyper-CHiDAM (n=2), IFE (n=4), methotrexate-cytarabine (n=3); [b]ESHAP (n=2), Hyper-CHiDAM (n=2); [c]ESHAP (n=1), methotrexate-L-asparaginase (n=1), ICE (n=1), IVE-MTX-dexamethasone (n=1), MACOP-HDMTX (n=1), MACOP-IVE-DHAP (n=1); [d]COPP-EBV-CAD (n=1). ASCT: autologous stem-cell transplantation; NOS: not otherwise specified; ALK: anaplastic lymphoma kinase; NK: natural killer; ECOG: Easter Cooperative Oncology Group; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CHOEP: cyclophosphamide, doxorubicin, etoposide; vincristine, and prednisolone; MACOP-B: methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; VACOP-B: etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; COPP-EBV-CAD: cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, solumedrol, cytarabine, and cisplatin; HDMTX: high-dose methotrexate; Hyper-CHiDAM: hyperfractionated cyclophosphamide, high-dose arabinosylcytosine, and high-dose methotrexate; ICE: ifosfamide, carboplatin, etoposide; IFE: ifosfamide, etoposide; IVE-MTX: ifosfamide, epirubicin, etoposide, and methotrexate.

months), PFS was significantly higher in the transplant group (Figure 2), 63% (95% confidence interval [95% CI]: 53.2-72.8) *vs*. 49% (95% CI: 37.2-60.8) at 5 years, with a median not reached (95% CI: not estimable) in the ASCT group *vs*. 50.5 months (95% CI: 0-110.9) in the non-ASCT group (*P*=0.042). The OS was also better in the transplant group, 74% (95% CI: 65.2-82.8) *vs*. 62% (95% CI: 50.0-73.9) at 5 years, with a median not reached (95% CI: not estimable) in the ASCT group *vs*. 100.6 months (95% CI: 66.1-135.1) in the non-ASCT group, although the difference was not statistically significant (*P*=0.124).

In the univariate analysis (Table 2), first-line transplantation was the only factor significantly associated with PFS, whereas stage and number of extranodal sites were the only factors associated with OS. Other variables that were not associated (*P*>0.05) with PFS or OS were sex, age, histology, performance status according to Easter Cooperative Oncology Group (ECOG), LDH, bone marrow infiltration, B symptoms, IPI, PIT score, chemotherapy regimen, and radiotherapy (Table 2).

We performed additional univariate analyses to assess the impact of ASCT on OS by subgroups, as shown in *Online*

Supplementary Table S1. We only detected statistically significant differences in the subgroup of patients with advanced-stage disease. Although transplantation does not seem to improve survival significantly in patients with localized stage at diagnosis, this was not the case among patients with advanced-stage disease, as shown in Figure 3. In this group of patients, OS was significantly longer for ASCT patients (median not reached [95% CI: not esti-

Table 2. Univariate analysis of progression-free survival and overall survival.

Characteristic	N	5-year PFS, %	*P*	5-year OS, %	*P*
Sex					
Male	104	56	0.427	69	0.510
Female	70	59		69	
Histological diagnosis					
PTCL, NOS	67	58		67	
AITL	48	49	0.220	65	0.199
ALCL, ALK-negative	38	68		81	
Others	21	53		63	
Age					
≤60 years	143	59	0.303	68	0.778
>60 years	31	50		73	
ECOG-PS					
0-1	144	58	0.435	69	0.447
2-4	27	55		70	
Lactate dehydrogenase					
Normal	86	59	0.478	72	0.227
Increased	76	55		66	
Ann-Arbor stage					
I-II	51	62	0.191	**80**	**0.034**
III-IV	122	55		**64**	
Extranodal sites					
0-1	142	59	0.219	**72**	**0.028**
≥2	32	49		**57**	
Bone marrow infiltration					
Yes	48	53	0.270	62	0.190
No	124	59		72	
B symptoms					
Yes	79	55	0.439	64	0.141
No	91	60		73	
International Prognostic Index					
0-1	79	59	0.058	72	0.089
2-3	70	59		70	
4-5	16	36		53	
Prognostic Index for T-cell Lymphoma					
0-1	119	60	0.334	71	0.450
2	32	51		67	
3-4	18	55		65	
First-line treatment					
CHOP-like	126	54	0.606	70	0.505
Others	48	65		67	
Radiotherapy					
Yes	22	45	0.229	63	0.522
No	152	59		70	
First-line ASCT					
Yes	103	**63**	**0.042**	74	0.124
No	71	**49**		62	

PFS: progression-free survival; OS: overall survival; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; ASCT: autologous stem-cell transplantation.

mable], 5-year OS 70% [95% CI: 59.8–80.2]) than for non-ASCT patients (median 71.0 months [95% CI: 40.3-101.7], 5-year OS 50% [95% CI: 32.0–68.0], *P*=0.028).

Multivariate analysis

To account for disease imbalances between groups, a multivariate analysis using Cox regression was performed. In 156 cases for which complete data were available, first-line ASCT was associated with significantly prolonged PFS (HR=0.57, 95% CI: 0.35-0.93) and OS (HR=0.57, 95% CI: 0.33-0.99) independently of the individual variables of the IPI and PIT scores, B-symptoms, sex, histological subtype, and first-line regimen, as shown in Table 3. Localized stage at diagnosis was also associated with better PFS (HR=0.54, 95% CI: 0.31-0.96) and OS (HR=0.38, 95% CI: 0.19-0.78). We also tested IPI and PIT scores (excluding all individual variables other than disease stage) in the multivariate analysis. First-line ASCT and localized stage at diagnosis maintained an independent influence on both PFS (HR=0.55 [95% CI: 0.34-0.90] and 0.52 [95% CI: 0.29-0.93] for ASCT and stage, respectively) and OS (HR=0.53 [95% CI: 0.31-0.91] and 0.40 [95% CI=0.20-0.80] for ASCT and stage, respectively).

In addition, we carried out a multivariate sensitivity analysis including only patients with nodal PTCL (angioimmunoblastic T-cell lymphoma, ALCL, ALK-negative and PTCL, NOS). First-line ASCT and localized stage at diagnosis maintained their independent influence on both PFS (HR=0.57 [95% CI: 0.34-0.96] and 0.45 [95% CI: 0.23-0.87] for ASCT and stage, respectively) and OS (HR=0.52 [95% CI: 0.29-0.93] and 0.31 [95% CI: 0.13-0.70] for ASCT and stage, respectively).

Separate analysis of patients in partial response after first-line

As a secondary objective, we assessed survival in patients

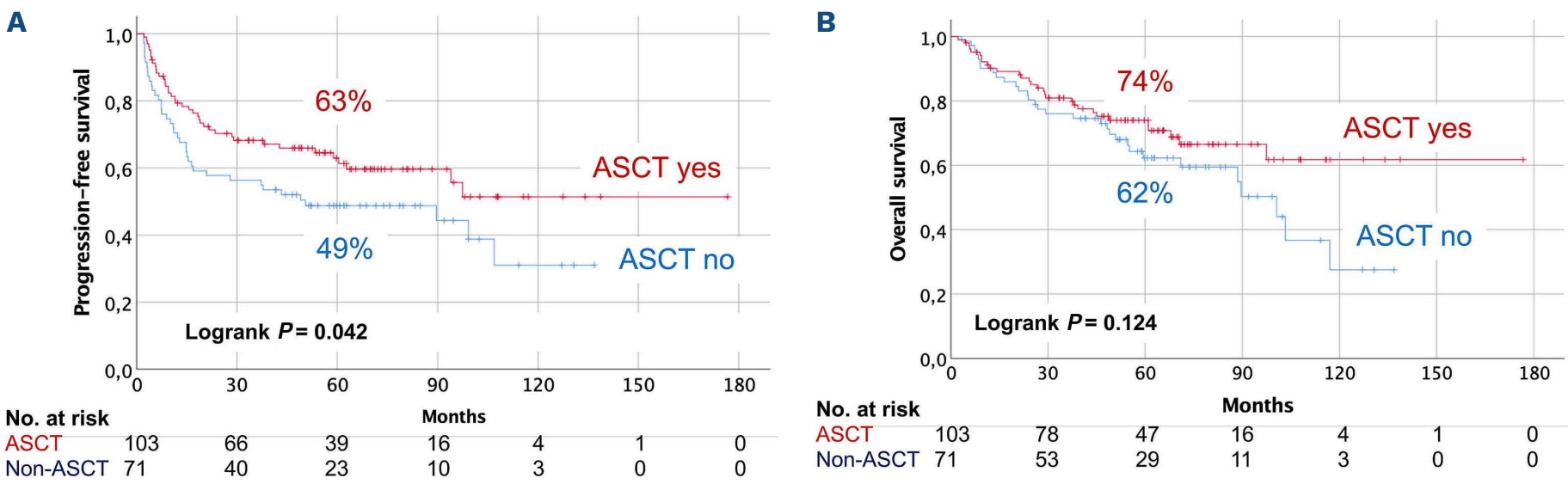

Figure 2. Kaplan–Meier estimation of survival in the transplanted and non-transplanted cohorts. (A) Progression-free survival; (B) overall survival. ASCT: autologous stem-cell transplantation

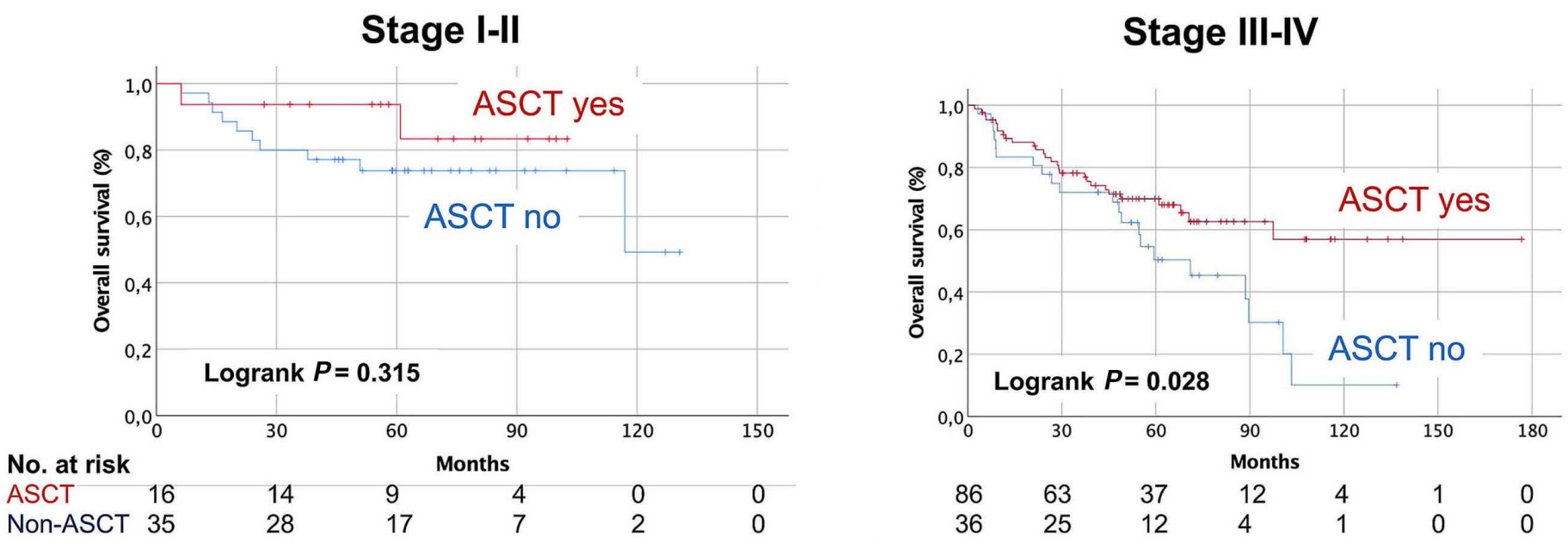

Figure 3. Kaplan-Meier estimation of overall survival by stage at diagnosis in the transplanted and non-transplanted cohorts. ASCT: autologous stem-cell transplantation.

undergoing ASCT in PR after first-line chemotherapy. Of 53 patients with a documented PR after first-line treatment, 15 were excluded because they had disease progression within 3 months of the initiation of the last cycle of first-line treatment. Fifteen patients underwent ASCT in PR after first-line treatment, whereas 23 patients did not undergo transplantation. Of these 23 patients, 17 received salvage chemotherapy while in PR and five received it after further progression. Eleven patients underwent transplantation (8 autologous and 3 allogeneic transplants) as part of the salvage therapy.

There were no significant differences between ASCT and non-ASCT groups with respect to patients' characteristics and first-line treatment, as shown in *Online Supplementary Table S2*. With a median follow-up of 84.1 months (range, 26.3-138.7 months), there was a trend towards better PFS in the transplant group compared with the non-ASCT group (*Online Supplementary Figure S1*): 46% (95% CI: 18.5-74.1) *vs*. 27% (95% CI: 7.7-45.3) at 5 years (*P*=0.081), respectively, with no significant differences in OS (53% [95% CI: 24.4-82.4] *vs*. 52% [95% CI: 31.8-72.6] at 5 years [*P*=0.962] in the ASCT and non-ASCT groups, respectively).

Discussion

In the present study, we collected clinical data from patients with newly diagnosed PTCL from 44 institutions in Spain and Italy. The cohorts included in this analysis either underwent upfront ASCT or were observed after achieving first CR/CRu (CR1). Although the clinical characteristics of the transplanted and non-transplanted patients differed, multivariate analysis identified ASCT as one of the main variables influencing PFS (HR=0.57, 95% CI: 0.35-0.93) and OS (HR=0.57, 95% CI: 0.33-0.99), suggesting a benefit of upfront ASCT in patients with PTCL in CR1.

The current recommendation to consider ASCT in first remission for most PTCL subtypes is largely based on the results from several phase II, single-arm studies.[4-8] The

Table 3. Multivariate Cox regression model (backward selection) for survival.

Characteristic (N=156)	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Included in the model				
First-line ASCT Yes *vs.* no	0.59 (0.36-0.96)	0.035	0.57 (0.33-0.99)	0.048
Stage I-II *vs.* III-IV	0.53 (0.29-0.96)	0.035	0.40 (0.19-0.81)	0.012
Removed from the model				
Sex Male *vs.* female		0.407		0.706
Histology PTCL, NOS *vs.* AITL *vs.* ALCL, ALK-negative *vs.* others		0.366		0.402
B symptoms Yes *vs.* no		0.986		0.528
Bone marrow infiltration No *vs.* yes		0.608		0.729
Age ≤60 *vs.* >60 years		0.997		0.281
ECOG-PS 0-1 *vs.* 2-4		0.617		0.779
Lactate dehydrogenase Normal *vs.* high		0.928		0.882
Extranodal sites 0-1 *vs.* ≥2		0.514		0.199
First-line chemotherapy CHOP-like *vs.* others		0.668		0.595
Radiotherapy Yes *vs.* no		0.188		0.135

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; 95% CI: 95% confidence interval; ASCT: autologous stem-cell transplantation; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

largest prospective trial evaluating ASCT in first-line was carried out by the Nordic Lymphoma Group (NLG T-01 study) in which patients with *de novo* PTCL were treated with CHOEP-14 x 6 followed by BEAM/BEAC and ASCT, leading to long-term PFS in 44% of patients.[8] In the Italian experience, patients who attained CR before ASCT had significantly better outcomes than patients who did not achieve CR, in terms of OS (48% *vs*. 22% at 10 years, *P*<0.0001) and event-free survival (47% *vs*. 11%, *P*<0.0001). However, these studies are very difficult to interpret because they did not include a control group of patients who did not undergo transplantation. In the absence of randomized clinical trials, no definitive consensus has therefore been reached about the role of ASCT as upfront consolidation for PTCL patients.

Retrospective comparisons of ASCT *versus* observation in first remission have produced conflicting results.[1,9,11-15] Fossard *et al*.[9] analyzed a cohort of 269 patients with nodal PTCL other than ALK-positive ALCL in CR (n=217) or PR (n=52) after induction. The patients were divided into two groups, ASCT and non-ASCT, based on the physicians' decision before starting induction treatment (intention-to-treat), according to the information collected in the medical records. Neither the Cox multivariate model nor the propensity score analysis revealed a survival advantage for ASCT as a consolidation procedure for patients in response after induction. However, in a study from the Swedish Lymphoma Registry,[1] upfront ASCT was associated with a superior OS (HR=0.58, *P*=0.004) and PFS (HR=0.56, *P*=0.002) compared with the outcomes of patients treated without ASCT in an intention-to-treat analysis of 252 patients with nodal PTCL or enteropathy-associated T-cell lymphoma (excluding ALK-positive ALCL), although no adjustment for response status after induction was made.

The design of our study differs from that of the two previously mentioned, since we selected the patients in CR1, who are likely to benefit the most from ASCT, rather than using a design that enabled an analysis based on the intention to treat. Since transplantation is usually performed several weeks after remission is achieved, rather than immediately after, patients who experienced progressive disease within 3 months of the initiation of the last cycle of first-line chemotherapy were not considered to be responders, and were excluded from the analysis to limit a potential bias. Other retrospective studies have also analyzed the role of ASCT in patients who achieve CR after induction treatment. Abramson *et al*.[13] showed a benefit favoring ASCT in first remission, but this disappeared in multivariate analysis when adjusting for CR to initial chemotherapy as well as stage, LDH, and hypoalbuminemia, although these results were limited by the small number of patients who proceeded to transplantation (n=33). In a single-center study[11], upfront ASCT did not improve PFS when compared with active observation in PTCL patients who achieved CR1 after receiving CHOP-like induction chemotherapy, but these results were also limited by the small sample size (n=20 transplanted patients). In contrast, in another observational study (COMPLETE)[14] that directly compared the outcomes of ASCT and non-ASCT in patients with nodal PTCL in CR1, ASCT emerged as one of the variables most strongly associated with favorable OS (HR=0.37; 95% CI: 0.15-0.89), whereas an advanced stage was associated with poor OS (HR=2.65; 95% CI: 1.08-6.55), in line with our results. However, this study was limited not only by the small number of patients who proceeded to transplantation (n=36), but also by the relatively short duration of follow-up (median of ~34 months).

Similar to the COMPLETE study, the present study directly compared the results of ASCT and non-ASCT in patients in CR1, but in a much larger series (103 ASCT and 71 non-ASCT cases) and with longer follow-up (>60 months). In our series, clinical characteristics differed between the two groups, as a significantly higher proportion of patients in the transplant group had adverse prognostic factors, such as advanced stage or increased LDH level. This indicates that baseline risk factors, especially stage, could play a significant role in determining whether to proceed with ASCT in CR1. Nevertheless, it is remarkable that the ASCT group was associated with superior PFS in the overall series, even though a significantly higher proportion of patients in the ASCT group had more adverse prognostic factors than the non-ASCT group. Consistent with what Park *et al*. found in the COMPLETE study,[14] in our study we observed a significant influence of upfront ASCT on OS, especially in patients with advanced-stage disease, whereas the benefit was less evident in patients with limited-stage disease. These results should be interpreted with caution because of the small sample sizes available for these subanalyses.

As a secondary objective, we assessed the survival of patients undergoing ASCT in PR after first-line therapy. Our results indicate that a significant proportion of patients in PR could benefit from transplantation, although, once again, these results must be interpreted with caution due to the very small sample size investigated in this subanalysis. Recent studies[16,17] have shown that patients with relapsed or refractory diffuse large B-cell lymphoma in PR after salvage therapy could still benefit from ASCT, but, to our knowledge, this subject has not been specifically investigated in patients with PTCL; it warrants being addressed in future studies.

In all the studies that we have discussed, including our own, the response to induction therapy is assessed mainly by computed tomography.[18] The impact of upfront ASCT in patients with PTCL in complete metabolic response has not been rigorously investigated. In a retrospective study,

the prognostic significance of ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (PET/CT) responses to induction chemotherapy was studied in 96 patients with PTCL from two centers. In the 59 patients with final response Deauville scores of 1–2, there was no statistically significant difference in the PFS and OS between the transplanted and non-transplanted patients. In addition, of the 37 patients with a final PET/CT response score of 3–4, the PFS rate was equally poor in transplanted and non-transplanted patients. The study was limited by the small number of patients who proceeded to transplantation in the overall series (n=37) and by the interpretation of the Deauville scale, since only patients with a score of 1–2 were considered to have shown a complete metabolic response, whereas the international consensus regards patients with scores of 1–3 as showing a complete response.[19,20] Therefore, further studies are needed to define the role of PET/CT in patients with PTCL treated with upfront ASCT.

The observational nature of this study means that it is prone to unintentional bias and the effects of confounding variables. There are three major limitations to the study. First, no central histological diagnostic review was undertaken. Second, in the non-ASCT group, the decision not to proceed to transplantation was taken well into the treatment of some patients, based mainly on the patients' general condition, which could have been associated with subsequent worse survival. Finally, the response to first-line treatment was determined by the treating physician supported by an imaging investigation; however, response criteria could have changed over time and imaging investigations were not specifically reviewed for this study.

Overall, and bearing in mind the study's limitations, the data presented here support the use of ASCT as a consolidation strategy for patients with PTCL other than ALK-positive ALCL in CR1. Our analyses suggest that some subgroups of patients, especially those with advanced-stage disease, might benefit more than others. Given the limitations of any retrospective study and the lack of consensus about the procedure, a large collaborative randomized trial should be conducted to enable definitive conclusions to be drawn.

Disclosures

AMG-S reports consulting fees, honoraria and/or non-financial support from Roche, Celgene/BMS, Morphosys, Kyowa Kirin, Clinigen, Eusa Pharma, Novartis, Gilead, Servier, Incyte, Janssen and Takeda. SN reports honoraria from Takeda. CP reports consulting fees, honoraria and/or non-financial support from Roche, Janssen, Celgene/BMS, Incyte and Kyowa Kirin. J-MS reports consulting fees and/or honoraria from Roche, Janssen, Gilead-Kite, BMS-Celgene, Novartis, Lilly, Incyte, Beigene and Takeda. RA reports consulting fees, honoraria and/or non-financial support from Takeda, Eusa Pharma and Novartis. SB reports honoraria and/or non-financial support from Gilead, Janssen, Novartis and Roche. The remaining authors have no relevant conflicts of interest to disclose.

Contributions

AMGS, DC, MB and MF were responsible for the design and conduct of the study; AMGS, MLP, MC, and MB analyzed and interpreted the data; AMGS drafted the report, which all co-authors critically revised for significant scientific content; MLP, GG, SN, CP, LP, AG, ID, MBO, JMS, MJR, JMM, EC, AIJU, IJ, LO, EGT, CM, AD, RA, NH, MJP, JLJ, MS, AR, SGV, and SB contributed research data to the study; all co-authors contributed to data analysis and interpretation, and approved the submitted and final versions.

Acknowledgments

AWe are grateful to Ángel Cedillo and Ana Méndez, from the Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea (GELTAMO), and Fondazione Italiana Linfomi (FIL), for their research support. Our thanks to Phil Mason for correcting the grammar and spelling errors of this article.

Data-sharing statement

Any requests for study data and protocol will be reviewed by the study management group and GELTAMO/FIL. Only requests that have a methodologically sound basis and whose proposed use of the data has been approved by the applicable ethics committees and regulatory authorities will be considered.

Collaborators

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