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*Annals of Oncology* 29: 715–723, 2018
doi:10.1093/annonc/mdx787
Published online 15 December 2017

ORIGINAL ARTICLE

# Role of up-front autologous stem-cell transplantation in peripheral T-cell lymphoma for patients in response after induction: an analysis of patients from LYSA centers

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Note: This study was previously presented in part in oral sessions at the 14th International Conference on Malignant Lymphoma (ICML), Lugano, Switzerland, 14–17 June 2017.

**Background:** Peripheral T-cell lymphoma (PTCL) remains a therapeutic challenge. Due to the rarity and the heterogeneity of PTCL, no consensus has been achieved regarding even the type of first-line treatment. The benefit of autologous stem-cell transplantation (ASCT) is, therefore, still intensely debated.

**Patients and methods:** In the absence of randomized trials addressing the role of ASCT, we performed a large multicentric retrospective study and used both a multivariate proportional hazard model and a propensity score matching approach to correct for sample selection bias between patients allocated or not to ASCT in intention-to-treat (ITT).

**Results:** Among 527 patients screened from 14 centers in France, Belgium and Portugal, a final cohort of 269 patients ≤65 years old with PTCL-not otherwise specified (NOS) ($N = 78$, 29%), angioimmunoblastic T-cell lymphoma (AITL) ($N = 123$, 46%) and anaplastic lymphoma kinase-positive anaplastic large cell lymphoma (ALK-ALCL) ($N = 68$, 25%) with partial ($N = 52$, 19%) or complete responses ($N = 217$, 81%) after induction was identified and information about treatment allocation was carefully collected before therapy initiation from medical records. One hundred and thirty-four patients were allocated to ASCT in ITT and 135 were not. Neither the Cox multivariate model (HR = 1.02; 95% CI: 0.69–1.50 for PFS and HR = 1.08; 95% CI: 0.68–1.69 for OS) nor the propensity score analysis after stringent matching for potential confounding factors (logrank $P = 0.90$ and 0.66 for PFS and OS, respectively) found a survival advantage in favor of ASCT as a consolidation procedure for patients in response after induction. Subgroup analyses did not reveal any further difference for patients according to response status, stage disease or risk category.

**Conclusions:** The present data do not support the use of ASCT for up-front consolidation for all patients with PTCL-NOS, AITL, or ALK-ALCL with partial or complete response after induction.

**Key words:** peripheral T-cell lymphoma, autologous stem-cell transplantation, propensity score matching, complete response, partial response, first line

## Introduction

Peripheral T-cell lymphoma (PTCL) encompasses a broad range of post-thymic (i.e. mature) subentities as defined by the 2008 WHO classification [1] and its recent revised version [2]. The most common entities are PTCL not otherwise specified (NOS) or angioimmunoblastic T-cell lymphoma (AITL), each representing approximately 20%–25% of mature T- and NK/T-cell lymphomas according to the International PTCL project and recent reports [3–6]. Compared with their B-cell counterparts, most PTCLs confer dismal prognosis. In fact, except for anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), 10-year overall survival (OS) for patients with PTCLs barely exceeds 15% [4]. Given the infrequency and the heterogeneity of these malignancies, no real consensus on first-line treatment has been established for most PTCLs [7]. Most medical teams worldwide use a cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-based regimen because no other combination has demonstrated clear superiority over this regimen [4, 8]. The addition of etoposide might be beneficial, at least for a subset of young patients with normal lactate dehydrogenase (LDH) values [9, 10]. Prognosis using this approach remains poor, as confirmed by a meta-analysis of 2815 patients treated with a CHOP or CHOP-like regimen, which found a 5-year OS of 38.5% for all PTCLs [11].

Furthermore, the place of autologous stem-cell transplantation (ASCT) as a consolidation procedure for first-line patients achieving a partial or complete response (PR and CR, respectively) is still highly debated [12–14]. Several nonrandomized prospective studies demonstrated consistent results regarding the impact of autologous stem transplantation in the first-line setting (see online-only extended bibliography). The number of patients with PTCLs enrolled in those studies varied from 26 to 166, and ALK + ALCL patients were excluded from most of them. Apart from prospective studies, most series supporting the use of ASCT in first-line settings were based on uncontrolled retrospective data (see online-only extended bibliography). Furthermore, they were highly heterogeneous with respect to line of therapy (first or subsequent), histology subtype (usually without precision regarding ALK status) and patient selection (only patients undergoing the procedure were included in most of them). All studies suffer from both positive and negative biases since patients undergoing ASCT are usually fitter, younger and in response to induction regimen but present with more aggressive disease features than patients not undergoing ASCT. The precise role of stem-cell transplantation for PTCLs, therefore, remains largely unknown in front-line settings, mainly due to inherent patient selection bias and low numbers of patients.

The lack of any randomized data to address the precise role of autologous transplantation in first-line therapy for young patients with PTCL-NOS, ALK-ALCL and AITL prompted us to conduct a large multicentric and international retrospective study. Only young patients (i.e. <65 years) in partial or complete response were considered to mitigate the strongest confounding bias in all previously published prospective and retrospective studies, that is the response achievement and quality after induction.

## Methods

### Patients, data collection and response assessment

All patients between 18 and 65 years old diagnosed with ALK-ALCL, PTCL-NOS or AITL between 1 January 2000 and 31 December 2015, from 14 centers in France, Belgium and Portugal were identified from local databases. Histological diagnosis was made by expert hematopathologists. Treatment choice for induction and consolidation (ASCT or observation) was made by local physicians in each center. There was no institutional policy as to whether all patients from a same center should receive ASCT or not. Data were retrospectively collected from medical records in all centers. The intention-to-treat (ITT) decision for ASCT at the time of therapy initiation was abstracted either from the initial medical report or the report from the multidisciplinary meeting before the start of treatment. Importantly, ITT could be precisely determined for all patients in the study before treatment initiation. The response assessment was determined at the end of induction treatment based on the International Working Group (IWG) criteria [15]. Since ASCT procedure arrangement usually takes a few weeks to proceed, only patients with a response duration lasting at least 3 months were considered as responders in the study. For patients with bone marrow involvement at diagnosis, all patients except two had a new biopsy at the end of induction to confirm or not the complete response status. If no marrow reassessment was performed, the patient was considered in partial response only (PR). Computed tomography (CT) scanner images and tumor response were analyzed and assessed by local radiologists. No patient with partial response received further treatment.

### Statistical analysis

Chi-square or Fischer's exact tests were used for statistical comparison of categorical variables. Age distributions were compared using the Mann–Whitney test. OS was calculated from the date of induction therapy until either the date of death from any cause or the date of the last contact. Progression-free survival (PFS) was measured from the date of induction therapy initiation to either the date of death from any cause, the date of progression or the date of last contact. Since subsequent treatment was administered only in case of disease progression, event-free survival (EFS) considering new treatment as an event was identical to PFS. Survival curves were constructed using the Kaplan–Meier method and were compared using the log-rank test [16]. The Cox proportional hazards regression model was used to assess the effect of multiple variables on OS and PFS [17]. All imbalanced parameters between the ASCT ITT and no-ITT groups were incorporated into the model along with age and histology subtypes. Propensity score matching (PSM) was carried out with a 1 : 1 case : control ratio. The nearest-neighbor matching method was used with a stringent caliper equal to 0.05 of the standard deviation of the logit of the PSM (MatchIt Package version 2.4-21, R software). PSM analysis accounted for age, LDH, PS, stage, B symptoms, histology, induction regimen and response quality for matching. All other tests were two-sided, and a *P*-level of 0.05 was considered as statistically significant. Analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC), R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/) and SPSS version 20 for Mac (SPSS, Chicago, IL).

## Results

### Patient characteristics

From the initial population of 527 patients, 269 of 471 patients with evaluable response status at the end of induction were responders (i.e. 57%) and were thus taken into account in the

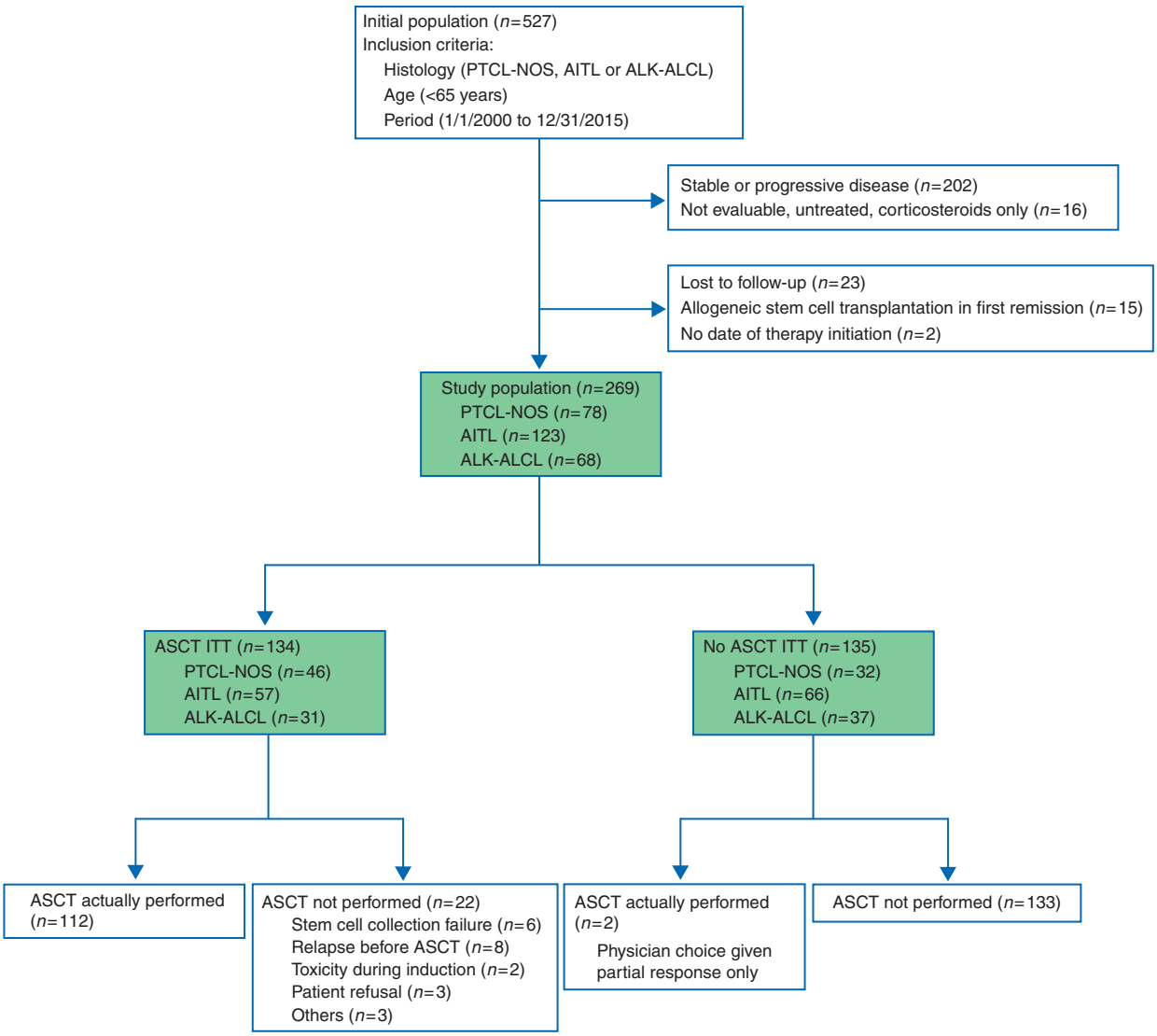


**Figure 1.** Study flowchart.

present study. The final study population comprised 269 young (i.e. ≤65 years old) patients with CR or PR at the end of the induction treatment (Figure 1). A vast majority of them (81%) were in CR. Twenty-nine percent of patients had PTCL-NOS ($N = 78$), 46% had AITL ($N = 123$) and 25% had ALK-ALCL ($N = 68$). By ITT, ASCT was chosen by a local physician as a consolidation procedure for 50% of patients ($N = 134$). Eventually, 22 patients did not undergo ASCT. Among them, there were six stem-cell collection failures. Eight patients who had responded for at least 3 months as per inclusion criteria relapsed just before starting conditioning regimen. The absence of a global consensus and recommendation regarding the use of up-front ASCT in PTCL was reflected by the heterogeneity of actual practice according to period of diagnosis and the hematology center (supplementary Figure S1, available at *Annals of Oncology* online). Patient characteristics according to ASCT ITT are summarized in Table 1. Briefly and as expected, patients who were allocated to ASCT in ITT by local physician presented with more aggressive disease. Hence, B symptoms, advanced stage disease, extranodal involvement and elevated LDH were observed significantly more frequently and resulted in higher age-adjusted International Prognostic Index (aaIPI) and lower CR rates in this patient group ($P = 0.002$ and $P = 0.028$, respectively). No significant difference was noted concerning patient age, histology subtype, bone marrow involvement, induction regimen, or PIT. Of note, positron emission tomography–computed tomography (PET-CT) scanner was performed for 119 patients out of 269. All patients except one considered in CR based on the IWG [15] criteria ($N = 101$) were PET-negative. Among the 18 patients evaluated by PET-CT scanner and in PR only using standard CT, 5 were reclassified as in CR. Median time from response assessment to ASCT was 1.5 months (range, 0.2–4.9) and conditioning regimen was BEAM for all patients except four (cyclophosphamide and total body irradiation, three patients; CCNU instead of BCNU for one patient).

## Survival

Median follow-up for surviving patients ($N = 163$) was 4.8 years. Among those, only eight patients had a follow-up shorter than 1 year. The median PFS was 3.7 years, and the median OS was

**Table 1. Patient characteristics according to ASCT in intention-to-treat**

| | Missing Data (*N*) | *N* (%)[a] ASCT ITT No (*N* = 135) | ASCT ITT Yes (*N* = 134) | *P* |
|---|---|---|---|---|
| Age, years | 0 | | | 0.25 |
| Mean (minimum–maximum) | | 53 (19–65) | 52 (19–66) | |
| Histology | 0 | | | 0.15 |
| PTCL-NOS | | 32 (24) | 46 (34) | |
| AITL | | 66 (49) | 57 (43) | |
| ALK-ALCL | | 37 (27) | 31 (23) | |
| Sex | 0 | | | 0.031 |
| Female | | 48 (36) | 65 (48) | |
| Male | | 87 (64) | 69 (51) | |
| ECOG score | 4 | | | 0.39 |
| 0-1 | | 105 (80) | 100 (75) | |
| 2-4 | | 27 (20) | 33 (25) | |
| B symptoms | 18 | | | 0.001 |
| no | | 70 (55) | 42 (34) | |
| yes | | 58 (45) | 81 (66) | |
| Stage | 1 | | | <0.001 |
| I–II | | 35 (26) | 9 (7) | |
| III–IV | | 100 (74) | 124 (93) | |
| Bone marrow involvement | 4 | | | 0.85 |
| no | | 90 (67) | 88 (68) | |
| yes | | 45 (33) | 42 (32) | |
| Extranodal involvement | 2 | | | 0.038 |
| No | | 62 (46) | 45 (34) | |
| Yes | | 72 (54) | 88 (66) | |
| LDH | 12 | | | 0.009 |
| ≤UNL | | 58 (45) | 38 (30) | |
| >UNL | | 70 (55) | 91 (70) | |
| aaIPI | 15 | | | 0.002 |
| 0–1 | | 62 (49) | 38 (30) | |
| 2–3 | | 65 (51) | 89 (70) | |
| PIT | 15 | | | 0.10 |
| 0–1 | | 69 (54) | 56 (44) | |
| 2–4 | | 58 (46) | 71 (56) | |
| Response to induction | 0 | | | 0.028 |
| CR | | 116 (86) | 101 (75) | |
| PR | | 19 (14) | 33 (25) | |
| Time from response evaluation to ASCT[b], yrs | 0 | | | |
| Median (minimum–maximum) | | NA | 1.5 (0.2–4.9) | NA |
| Treatment | 0 | | | 0.14 |
| CHOP-like or CHOEP[c] | | 98 (73) | 108 (81) | |
| ACVBP or COPADM | | 30 (22) | 24 (18) | |
| Others[d] | | 7 (5) | 2 (1) | |

[a]Except for age (mean and range).
[b]When ASCT was actually performed.
[c]CHOP every 2 or 3 weeks ($n = 151$), CHOP + rituximab for some patients with AITL ($n = 21$), CHOP + alemtuzumab ($n = 4$) and CHOP + romidepsin ($n = 6$); CHOEP ($n = 24$ patients).
[d]Other regimens are DHAP (aracytine- and platine-based regimen), VIP-rABVD[8] and CVP (CHOP-like regimen without anthracyclines).
CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; COPADM, cyclophosphamide, vincristine, prednisone, doxorubicin and methotrexate; ASCT, autologous stem-cell transplantation; ITT, intention-to-treat; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALK-ALCL, anaplastic large cell lymphoma kinase-negative lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; UNL, upper normal limit; aaIPI, age-adjusted international prognostic index; PIT, prognostic index for T-cell lymphoma; CR, complete response; PR, partial response; NA, not applicable.

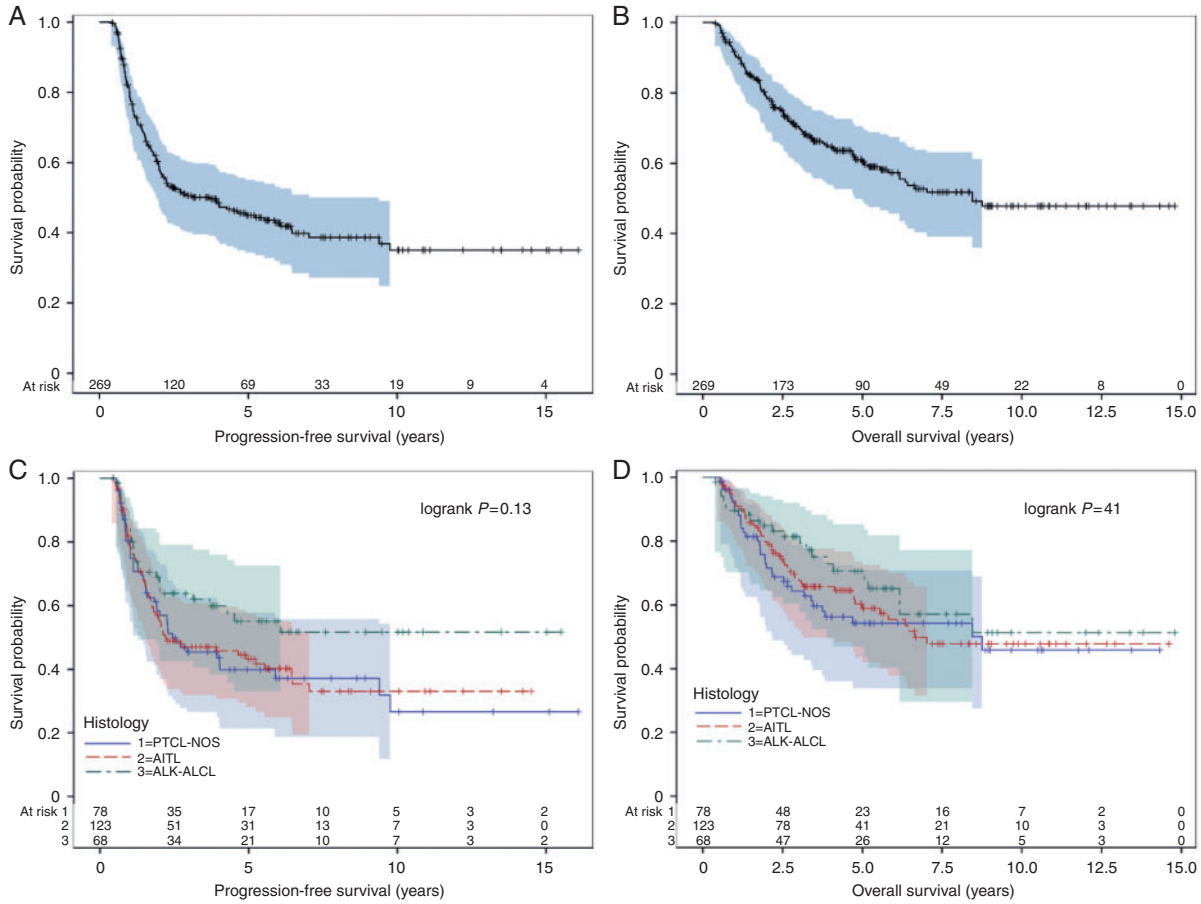


**Figure 2.** Survival of patients in response after induction. (A) Progression-free survival. (B) Overall survival. (C) Progression-free survival according to histological subtype. (D) Overall survival according to histological subtype.

8.4 years for the entire cohort (Figure 2A and B). At 5 years, PFS was 45.0% (95% confidence interval (CI): 37.8% to 50.6%), and OS was 60.4% (95% CI: 53.6% to 66.5%). Patients with ALK-ALCL experienced a slightly longer time to progression compared with patients with PTCL-NOS or AITL, although the difference did not reach significant difference (Figure 2C). No OS difference was observed according to histology subtype (Figure 2D).

## Multivariate analysis

To account for disease severity imbalances between ITT subgroups, a multivariate analysis using a Cox proportional hazard ratio regression model was performed. Based on 240 observations with fully available data, it demonstrated that only remission status (CR versus PR) at the end of induction was associated with significantly prolonged PFS and OS (Table 2). Patient allocation to ASCT in ITT was not associated with an improved outcome (HR = 1.02, 95% CI: 0.69–1.50 for PFS and HR = 1.08, 95% CI: 0.68–1.69 for OS). A model where aaIPI was replaced by its individual variables gave similar results (data not shown).

## Propensity score matching analysis

Patient age, disease severity and induction regimen are known potential confounding factors undermining the formal assessment of ASCT in first-line settings. To strengthen results from the multivariate Cox model, another approach using a propensity score matching analysis was performed based on the conditional probability of assigning patients to ASCT based on age, LDH, PS, stage, B symptoms, histology, induction regimen and response quality. The final matched population comprised 73 patients in each group with balanced propensity scores (supplementary Figure S2, available at *Annals of Oncology* online) and comparable baseline characteristics and response quality (Table 3). Only proportion of patients with bone marrow involvement was nearly significantly different ($P = 0.06$) but with a higher rate in the no-ASCT group.

No outcome difference was observed between the two groups regarding either PFS or OS ($P = 0.90$ and 0.66, respectively, Figure 3). At 5 years, PFS was 40.5% (95% CI: 28.0% to 52.6%) and 46.3% (95% CI: 34.1% to 57.6%); OS was 60.4% (95% CI: 46.7% to 71.6%) and 59.2% (46.1% to 70.1%) among patients without or with ASCT planned according to ITT, respectively. No difference according to the use of up-front ASCT in ITT was further noted when patients with advanced stage disease (III or IV), with aaIPI > 1 or reaching a PR only at the end of induction were considered (supplementary Figure S3, available at *Annals of Oncology* online for survival according to ASCT-ITT and response status).

## Causes of death

One hundred and six patients died during the follow-up. The main cause of death was disease progression ($N = 87$, 82%),

**Table 2. Multivariate Cox proportional hazard ratio regression model**

| | PFS[a] | | | OS[a] | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| B symptoms | | | | | | |
| Yes (versus no) | 1.18 | 0.78–1.79 | 0.41 | 0.89 | 0.55–1.44 | 0.65 |
| Histology | | | | | | |
| AITL (versus PTCL-NOS) | 0.97 | 0.62–1.51 | 0.89 | 0.97 | 0.58–1.63 | 0.92 |
| ALK- ALCL (versus PTCL-NOS) | 0.74 | 0.43–1.25 | 0.26 | 0.79 | 0.43–1.46 | 0.46 |
| Age, years | | | | | | |
| Continuous parameter | 0.99 | 0.97–1.01 | 0.56 | 1.01 | 0.99–1.04 | 0.15 |
| Sex | | | | | | |
| Male (versus female) | 1.42 | 0.97–2.06 | 0.07 | 1.21 | 0.79–1.87 | 0.37 |
| aaIPI | | | | | | |
| 1 (versus 0) | 1.31 | 0.61–2.84 | 0.48 | 1.27 | 0.50–3.20 | 0.60 |
| 2 (versus 0) | 1.53 | 0.71–3.29 | 0.27 | 1.45 | 0.57–3.66 | 0.42 |
| 3 (versus 0) | 1.72 | 0.72–4.09 | 0.21 | 1.83 | 0.65–5.13 | 0.24 |
| Response to induction | | | | | | |
| PR (versus CR) | 1.86 | 1.22–2.84 | 0.003 | 2.04 | 1.28–3.25 | 0.002 |
| ASCT ITT | | | | | | |
| Yes (versus no) | 1.02 | 0.69–1.50 | 0.89 | 1.08 | 0.68–1.69 | 0.74 |

[a]Models carried out on 240 observations with fully available parameters.

PFS, progression-free survival; OS, overall survival; AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; ALK-ALCL, anaplastic large cell lymphoma kinase-negative lymphoma; aaIPI, age-adjusted international prognostic index; PR, partial response; CR, complete response; ASCT ITT, autologous stem-cell transplantation in intention-to-treat; HR, hazard ratio; CI, confidence interval.

followed by fist-line treatment related mortality defined by death in first remission ($N = 12$, 11%), death in subsequent remission ($N = 5$, 5%) and unknown causes ($N = 2$, 2%). By ITT, no significant difference in terms of cause of death was observed between patients allocated to the ASCT group compared with the no-ASCT group ($P = 0.09$, supplementary Table S1, available at *Annals of Oncology* online). No further difference was observed when the group of patients actually receiving the ASCT procedure was considered compared with those who did not underwent ASCT ("per protocol" comparison). Four second malignancies were observed without any differences between sub-groups (supplementary Table S1, available at *Annals of Oncology* online). The absence of benefit for patients receiving ASCT in first remission was therefore not due to an increased toxicity related to the procedure.

## Discussion

In the absence of a randomized trial, no definitive agreement has been reached on the role of ASCT as an up-front consolidation strategy for patients with ALK- ALCL, AITL or PTCL-NOS in PR or CR after induction. A summary of selected prospective and retrospective publications specifically addressing the role of ASCT in PTCL in first line is presented in supplementary Table S2, available at *Annals of Oncology* online. ESMO recommendations and recent guidelines from a committee of the American Society for Blood and Marrow Transplantation currently propose ASCT as first-line therapy for transplant-eligible patients [18, 19]. NCCN guidelines (version 2.2017) recommend ASCT or observation for patients in CR and additional treatment followed by ASCT or allogeneic stem-cell transplantation for patients with PR. Based on a large multicenter and international cohort of patients with PR or CR after induction, we did not detect any survival advantage of ASCT over observation for patients achieving at least a partial response after induction.

The role of up-front ASCT as a consolidation therapy for patients with PTCL has been a critical question for years. Despite many prospective and retrospective studies addressing the issue, no definitive answer or broad consensus has been reached due to the lack of controlled trial (see online-only extended bibliography). A formal comparison between approaches is hampered by the fact that patients allocated to ASCT often present with more aggressive disease at diagnosis, while transplant-eligible patients are usually fitter or younger. Both retrospective and prospective uncontrolled published studies have suffered from several caveats precluding unbiased conclusions on the role of up-front ASCT. Hence, most retrospective studies did not assess ITT ASCT assignment but only included patients undergoing the procedure. In such studies, long-term survival of transplanted patients is usually not compared with survival of non-transplanted responders. In prospective uncontrolled studies, transplant-eligible patients are considered only, rendering any comparison with historical cohorts merely speculative.

To the best of our knowledge, this is the largest analysis carried out to evaluate the role of up-front ASCT in responder patients with PTCL. A recently published real-world data analysis from

**Table 3. Characteristics of the propensity score matched population**

| | Missing data (*N*) | *N* (%)[a] ASCT ITT No (*N* = 73) | ASCT ITT Yes (*N* = 73) | *P* |
|---|---|---|---|---|
| Age, years | 0 | | | 0.51 |
| Mean (minimum–maximum) | | 55 (19–65) | 55 (29–66) | |
| Histology | 0 | | | 0.41 |
| PTCL-NOS | | 19 (26) | 19 (26) | |
| AITL | | 43 (59) | 37 (51) | |
| ALK-ALCL | | 11 (15) | 17 (23) | |
| Sex | 0 | | | 0.09 |
| Female | | 44 (60) | 33 (45) | |
| Male | | 29 (40) | 40 (55) | |
| ECOG score | 0 | | | 0.85 |
| 0–1 | | 53 (73) | 51 (70) | |
| 2–4 | | 20 (27) | 22 (30) | |
| B symptoms | 0 | | | 0.73 |
| No | | 26 (36) | 29 (40) | |
| Yes | | 47 (64) | 44 (60) | |
| Stage | 0 | | | 1.00 |
| I–II | | 5 (7) | 6 (8) | |
| III–IV | | 68 (93) | 67 (92) | |
| Bone marrow involvement | 3 | | | 0.06 |
| No | | 39 (53) | 49 (70) | |
| Yes | | 34 (47) | 21 (30) | |
| Extranodal involvement | 0 | | | 0.86 |
| No | | 24 (33) | 26 (36) | |
| Yes | | 49 (67) | 47 (64) | |
| LDH | 0 | | | 0.59 |
| ≤UNL | | 25 (34) | 21 (29) | |
| >UNL | | 48 (66) | 52 (71) | |
| aaIPI | 0 | | | 0.85 |
| 0–1 | | 24 (33) | 22 (30) | |
| 2–3 | | 49 (67) | 51 (69) | |
| PIT | 0 | | | 0.73 |
| 0–1 | | 30 (41) | 33 (45) | |
| 2–4 | | 43 (59) | 40 (55) | |
| Response to induction | 0 | | | 1.00 |
| CR | | 62 (85) | 61 (84) | |
| PR | | 11 (15) | 12 (16) | |
| Treatment | 0 | | | 0.12 |
| CHOP-like or CHOEP | | 55 (75) | 63 (86) | |
| ACVBP or COPADM | | 16 (22) | 10 (14) | |
| Others | | 2 (3) | 0 (0) | |

For abbreviations, see Table 1.
[a]Except for age (mean and range).

the Swedish Lymphoma Registry found prolonged OS and PFS for transplanted patients with PTCL-NOS, AITL, ALK-ALCL and enteropathy-associated T-cell lymphoma after adjustment for potentially confounding factors in multivariate analysis [9]. However, the group of patients retrospectively allocated to the non-ASCT category in ITT might include a higher proportion of patients with early progression for whom ASCT could not have been considered. No adjustment on response status, the strongest bias in assessing the role of ASCT, was therefore conducted to rule out any imbalance between subgroups. Actually, a recently published series partially based on the same real-word registry did not find any survival advantage for ASCT in uni- or multivariate analysis when patients in CR only were considered [20]. In the present study, since only responders were enrolled

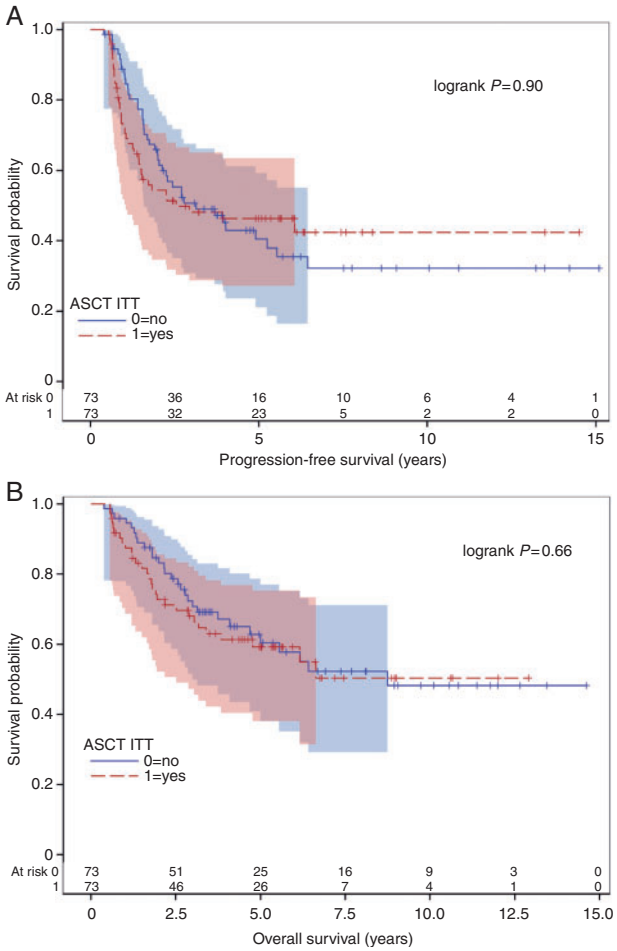


**Figure 3.** Propensity score matching survival analysis of patients in response after induction. (A) Progression-free survival of patients in the matched subset cohort. (B) Overall survival of patients in the matched subset cohort.

(ensuring that all patients survived at least until the end-of-induction without the need for a landmark time analysis), no selection bias undermined the outcome assessment. Supporting the significance of response quality in PTCL, CR achievement prevailed over any baseline prognosis factors in the multivariate model. In line with the present data, a recently published large retrospective multicenter US study showed that the survival advantage conferred by ASCT in a univariate analysis vanished after the adjustment for potentially confounding factors (i.e. CR to initial chemotherapy, stage, LDH, and hypoalbuminemia) [21].

Overall, 5-year PFS and OS for responders were 45% and 60%, respectively, without a significant difference according to ASCT in ITT. In PTCL-NOS and AITL, 5-year PFS and OS rates have been previously reported not to exceed 20% and 35%, respectively [4], confirming that primary refractoriness is one of the major concerns for patients with PTCL. Importantly, 57% of patients from the initially screened population were in CR (46%) or PR (11%) at the end of induction and were included in the study. This is in line with previously published studies where ALK + ALCL patients were excluded: 62% of ORR for the randomized study from Simon et al. [8] (<5% of patients with ALK + ALCL), 59% of ORR in the prospective series from Mercadal et al. [22] or 52% of CR in the retrospective work from Yam et al. [23]. Furthermore, one of the main inclusion criteria of the study was that response had to last at least 3 months to be considered. So, patients with very early relapse after induction were considered as primary refractory and were not enrolled in the study. This ensured that there was sufficient time to perform transplantation in the ASCT-ITT group to limit a potential bias disfavoring the procedure (median time from response assessment to ASCT was therefore 1.5 months). This could also explain why the proportion of responders is slightly lower than reported in other studies [24, 25]. Supporting the view that prognosis in PTCL is related to response to induction and not to the ASCT procedure itself, a recently published study from Tobinai and colleagues showed that 45% of patients <65 years in CR after induction were alive without disease at 5 years [26]. The figure is perfectly identical to the 45% 5-year PFS in our series of patients whether they were allocated to ASCT or not in ITT.

The present work suffers from some of the typical drawbacks of retrospective data collection. These disadvantages include the absence of histologic diagnosis and radiologic review, although there is no a priori reason this could favor a group of patients over the other. The extended inclusion period, the differing duration of follow-up and the lack of sufficient power to detect a limited outcome difference between ASCT and no further consolidation treatment have to be further acknowledged. Additionally, matching or statistical adjustment techniques cannot account for all confounding parameters and biases. We cannot rule out that other features of aggressive disease were not fully captured by baseline characteristics or response quality.

Notably, since only 24 patients received etoposide in addition to CHOP as an induction regimen, the specific role of the drug could not be statistically assessed in the present study. In addition, limited number of patients in each histological subgroup precluded reasonable evaluation of ASCT according to subtypes. Lastly, PET-CT was performed in roughly one-third of the cohort with a low number of discordant cases therefore precluding an analysis based on PET-CT response criteria compared with CT assessment.

It is generally acknowledged that ASCT can provide a long-term control of PTCL with a survival plateau after 5 years. However, the present study demonstrates that such a plateau can be achieved without the need for consolidation treatment of patients with a response following the induction regimen (Figure 3B). Moreover, all patient data were individually collected. The treatment allocation was determined before induction therapy was started, and the sample size was substantial, with homogeneous histological subtypes (PTCL-NOS versus AITL versus ALK-ALCL) and response statuses (PR or CR) underlying the strong quality control of the current study.

Overall, and in consideration of the study limitations, the data presented in this study do not support the use of ASCT as a consolidation strategy for all responding patients with PTCL-NOS, AITL or ALK-ALCL in first line. Further study is needed to precisely evaluate if a specific subgroup like patients with PET-defined PR, specific histologic or molecular subtype, might benefit from the procedure. Moreover, given the flaws of any retrospective data collection, the economic burden associated to ASCT in PTCL [27] and the absence of any consensus over the procedure, a large collaborative randomized trial should be undertaken to allow for a definitive answer.

## Funding

EB has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie (grant agreement N°661106), the Philippe Foundation (no grant number applies) and the Fulbright Program (Monahan Foundation) (no grant number applies).

## Disclosure

The authors have declared no conflicts of interest.

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