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ORIGINAL REPORT

Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01

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ABSTRACT

Purpose
Systemic peripheral T-cell lymphomas (PTCLs) respond poorly to conventional therapy. To evaluate the efficacy of a dose-dense approach consolidated by up-front high-dose chemotherapy (HDT) and autologous stem-cell transplantation (ASCT) in PTCL, the Nordic Lymphoma Group (NLG) conducted a large prospective phase II study in untreated systemic PTCL. This is the final report, with a 5-year median follow-up, of the NLG-T-01 study.

Patients and Methods
Treatment-naive patients with PTCL age 18 to 67 years (median, 57 years) were included. Anaplastic lymphoma kinase (ALK) –positive anaplastic large-cell lymphoma (ALCL) was excluded. An induction regimen of six cycles of biweekly CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) was administered (in patients age > 60 years, etoposide was omitted). If in complete or partial remission, patients proceeded to consolidation with HDT/ASCT.

Results
Of 166 enrolled patients, 160 had histopathologically confirmed PTCL. The majority presented with advanced-stage disease, B symptoms, and elevated serum lactate dehydrogenase. A total of 115 underwent HDT/ASCT, with 90 in complete remission at 3 months post-transplantation. Early failures occurred in 26%. Treatment-related mortality was 4%. At 60.5 months of median follow-up, 83 patients were alive. Consolidated 5-year overall and progression-free survival (PFS) were 51% (95% CI, 43% to 59%) and 44% (95% CI, 36% to 52%), respectively. Best results were obtained in ALK-negative ALCL.

Conclusion
Dose-dense induction followed by HDT/ASCT was well tolerated and led to long-term PFS in 44% of treatment-naive patients with PTCL. This represents an encouraging outcome, particularly considering the high median age and adverse risk profile of the study population. Therefore, dose-dense induction and HDT/ASCT are a rational up-front strategy in transplantation-eligible patients with PTCL.

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INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare lymphoid malignancies. In Western countries, they account for less than 15% of all lymphomas and less than 20% of all patient cases with aggressive histology.[1,2] The most common histopathologic PTCL subtypes are PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AILT), and anaplastic large-cell lymphoma (ALCL), with or without expression of the fusion protein nucleophosmin anaplastic lymphoma kinase (ALK). Most commonly, PTCL occurs in middle-age to elderly patients, with prognostically unfavorable clinical characteristics.[3] Conventionally treated PTCLs, with the exception of ALK protein–positive ALCL, have poorer outcomes than their B-cell counterparts.[3-7] The role of high-dose therapy (HDT) with autologous stem-cell transplantation (ASCT) as an up-front strategy in PTCL is still under investigation. Most data derive from small retrospective series, and their interpretation is complicated by heterogeneous histologic subtype frequencies and whether patients with ALK-positive ALCL were included. Results from these studies (such as those by Casulo et al[8] and Reimer[9]) are therefore not readily comparable. So far, only a few, mostly small, PTCL-restricted prospective trials evaluating up-front HDT/ASCT have been reported.[10-13]

This is the final analysis of the largest clinical trial conducted in systemic PTCL to our knowledge. We wanted to determine the efficacy of a dose-dense induction treatment followed by HDT/ASCT in previously untreated systemic PTCL. The patient cohort was large enough to allow histologic subtype analysis; it had a high pretherapeutic risk profile consistent with low selection bias and a median follow-up of sufficient length to enable an evaluation of both early and late failures.

PATIENTS AND METHODS

Patient Cohort

A total of 166 patients age 18 to 67 years with newly diagnosed systemic PTCL were enrolled between October 2001 and October 2007. A total of 24 centers from Denmark, Finland, Norway, and Sweden participated in this clinical trial of the Nordic Lymphoma Group (NLG-T-01). ALK-positive ALCL, primary cutaneous, and primary leukemic subtypes were excluded. Additional requirements for inclusion were: performance score (PS) < 4 (WHO), no severe comorbidity, no concomitant malignancy (nonmelanoma skin tumors and in situ cervical carcinoma excepted), HIV negativity, no uncontrolled infection, no pregnancy or lactation, and written informed consent. The study was approved by health authorities and ethics committees in all participating countries.

Pathology

Diagnoses were assessed according to the 2001 edition of the WHO classification of lymphoid neoplasms.[14] Pathologic review was performed at referral center level, on which treatment decisions were made. Diagnoses were subsequently (ie, post-therapeutically) reviewed again by national reference hematopathologists.

Treatment Schedule

After staging with whole-body computed tomography scan and bone marrow (BM) biopsy, patients were treated with three courses of biweekly chemotherapy supported by granulocyte colony-stimulating factor. The chemotherapy regimen consisted of cyclophosphamide 750 mg/m^2 intravenously (IV) on day 1, doxorubicin 50 mg/m^2 IV on day 1, vincristine 1.4 mg/m^2 (maximum, 2 mg) IV on day 1, etoposide 100 mg/m^2 IV on days 1 through 3, and prednisone 50 mg orally twice per day on days 1 through 5 (CHOEP-14). Because of reported excessive toxicity of biweekly CHOEP in elderly patients with diffuse large B-cell lymphoma,[15] etoposide was omitted (CHOP-14) in patients age > 60 years. Patients were restaged with computed tomography scan, and if pretherapeutically involved, BM was biopsied again. If found to be in partial (PR) or complete remission (CR),[16] patients received three additional courses of chemotherapy. The fifth and/or sixth course was used as stem-cell mobilizing chemotherapy. Granulocyte colony-stimulating factor was administered daily from day 1 after mobilizing chemotherapy until stem-cell harvest. A new restaging was performed after the sixth course of chemotherapy. For patients in PR or CR at the end of induction, HDT was initiated within the following 4 to 6 weeks and consisted of carmustine 300 mg/m^2 IV on day 1, etoposide 100 mg/m^2 twice per day IV on days 2 through 5, cytarabine 200 mg/m^2 IV twice per day on days 2 through 5, and melphalan 140 mg/m^2 IV on day 6 (BEAM; at Finnish centers, cyclophosphamide 6,000 mg/m^2 was administered instead of melphalan [BEAC]). Patients were removed from protocol in cases of stable (SD) or progressive disease (PD), unacceptable toxicity, or patient request.

Response Assessment and Time-to-Event End Points

Treatment response was assessed as CR, PR, SD, or PD according to previously reported criteria.[16] Response assessment took place at three predefined time points (ie, after three and six courses of CHOEP/CHOP and after HDT/ASCT). Lesions were measured bidimensionally. The following time-to-event end points were studied: overall survival (OS), progression-free survival (PFS), and time to treatment failure (TTF). Follow-up began on the start date of the first induction chemotherapy course and ended on November 30, 2009. OS was defined either as the time from diagnosis to death, if death occurred before November 30, 2009, or as the time from diagnosis to the end of follow-up. PFS was similarly defined as the time from diagnosis to either death or PD, whichever came first, or, if neither of these events occurred, the time from diagnosis to the end of follow-up. TTF was defined as the time to death, PD, or start of off-protocol treatment for any reason, whichever came first, or, in the absence of these events, the time from diagnosis to the end of follow-up.

Statistical Methods

Of the 166 patients registered in the study, six were excluded before treatment start for not fulfilling inclusion criteria. Therefore, a total of 160 patients with histologically confirmed PTCL constituted the intention-to-treat population (ITTP). Time-to-event end points were illustrated by means of Kaplan-Meier curves with 95% Greenwood confidence bands. Log-rank tests and Cox regression models were used to analyze the univariate and multivariate impacts of various prognostic factors. Treatment-related toxicity parameters are presented by means of descriptive statistical methods.

RESULTS

Clinicopathologic Features

The ITTP of 160 patients included: PTCL-NOS (n = 62; 39%), ALK-negative ALCL (n = 31; 19%), AILT (n = 30; 19%), enteropathy-associated T-cell lymphoma (EATL; n = 21; 13%), panniculitis-like T-cell lymphoma (n = 6; 4%), T-cell/natural killer (T/NK) nasal-type T-cell lymphoma (n = 5; 3%), and hepatosplenic T-cell lymphoma (n = 5; 3%). Two thirds of the patients were men, and the median age was 57 years (range, 22 to 67 years). Eighty-one percent of patients presented with advanced-stage disease, 59% with B symptoms, and 62% with elevated serum lactate dehydrogenase (Table 1). Seventy-one percent of all patients

Table 1. Pretherapeutic Clinicopathologic Patient Characteristics (n = 160)

Characteristic	Patients	
	No.	%
Age, years		
Median	57	
Range	22-67	
Sex		
Male	107	67
Female	53	33
B symptoms	94	59
Elevated sLDH	99	62
PS $\geq$ 2*	46	29
Bulk	26	17
Clinical stage III to IV	129	81
BM involvement	41	26
IPI $\geq$ 2	115	72
Histologic subtype		
PTCL-NOS	62	39
ALK-negative ALCL	31	19
AILT	30	19
EATL	21	13
Panniculitis like	6	4
T/NK nasal type	5	3
Hepatosplenic	5	3

Abbreviations: AILT, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; BM, bone marrow; EATL, enteropathy-associated T-cell lymphoma; IPI, International Prognostic Index; PS, performance score; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; sLDH, serum lactate dehydrogenase; T/NK, T cell/natural killer.
*According to WHO scale 0 to 4.

had a good PS (WHO 0 to 1) at inclusion. With regard to International Prognostic Index (IPI), the risk factor distribution was as follows: one factor, n = 45; two factors, n = 52; three factors, n = 30; and four to five factors, n = 33. The distribution of IPI risk groups among the three major histologic subtypes (ie, PTCL-NOS, AILT and ALCL) did not differ significantly (χ^2 test, $P = .24$).

Treatment Response

A flow chart of the study is shown in Figure 1. Of the 160 patients, 156 (97%) were assessable for treatment response. At the end of the induction schedule, 131 patients had achieved either CR/unconfirmed CR (CRu; n = 82) or PR (n = 49), corresponding to an overall response rate (ORR) of 82%. Primary refractory disease was observed in 25 patients (16%). Sixteen of the 131 responders went off protocol before HDT/ASCT because of infection (n = 5), mobilization failure (n = 2), pulmonary insufficiency (n = 2), intestinal perforation (n = 2), protocol violation (n = 2), PD before HDT/ASCT (n = 1), cachexia (n = 1), or psychiatric condition (n = 1). Removal of these patients, along with those with primary refractory disease, resulted in a total of 41 patients (ie, 26% of the ITTP) not reaching transplantation. Of the 131 responders, 115 (72% of the original ITTP) underwent HDT/ASCT. At 3 months post-transplantation, 90 patients (78% of those receiving transplants) had achieved CR/CRu and nine (8%) PR. There were two cases of transplantation-related death (septicemia and cerebrovascular hemorrhage). Another 28 patients (18%) relapsed/progressed within 2 years post-transplantation. Eleven patients (7% of the ITTP) experienced late relapse (ie, > 2 years post-transplantation; (range, 28 to 71 months). The latest relapse (71 months post-transplantation) was of ALK-negative ALCL histology. A clonality analysis performed at relapse revealed the same malignant clone as at presentation.

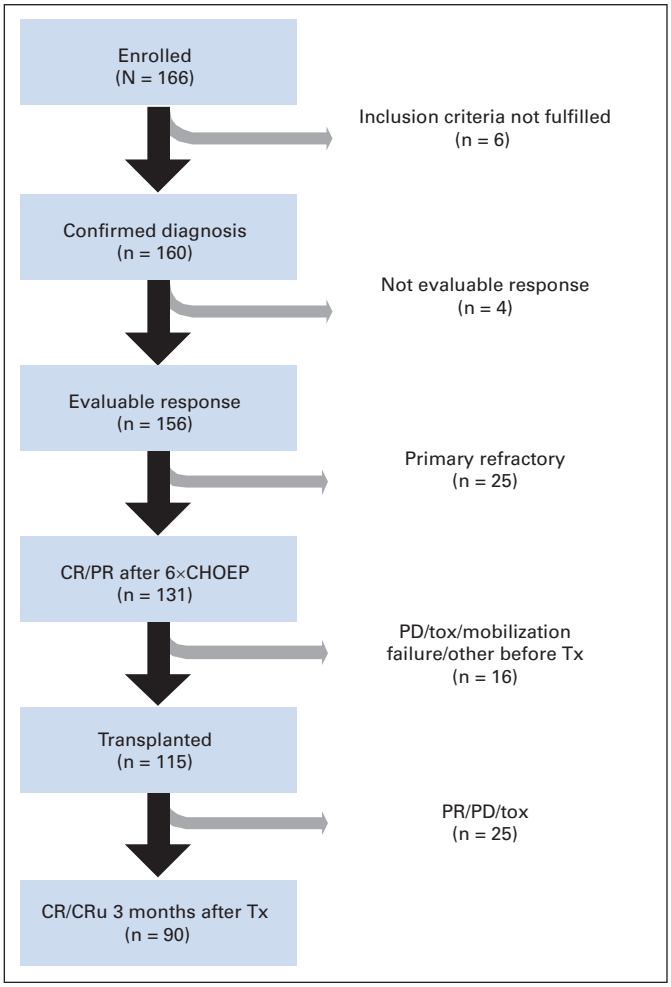

Fig 1. Flow chart of the NLG-T-01 (Nordic Lymphoma Group) study cohort showing the numbers and types of treatment failures and responding patients throughout the different stages of the protocoled treatment algorithm. CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; CR, complete remission; CRu, unconfirmed complete remission; PD, progressive disease; PR, partial remission; tox, toxicity; Tx, transplantation.

Toxicity

Pretransplantation grades 3 to 4 hematologic toxicities were seen in 86% of patients, whereas grades 3 to 4 nonhematologic toxicities were recorded in 72 patients (45%), with infectious complications as the most frequent adverse event (n = 59; 37%), followed by mucositis (n = 7; 4%) and GI toxicity (n = 6; 4%). Seven patients died as a result of treatment-related toxicity, corresponding to an overall treatment-related mortality of 4%. These seven deaths resulted from bacterial septicaemia (n = 4), virus-associated hemophagocytic syndrome (n = 1), GI bleeding (n = 1), and cerebrovascular hemorrhage (n = 1).

Follow-Up and Survival

Of all the 160 patients, 83 were alive at the time of analysis. The median follow-up of surviving patients was 60.5 months (range, 26.4 to 96.3 months). For half of the ITTP (80 patients), follow-up was 5 to 8 years, and for an additional 35% (60 patients), it was 3 to 5 years. A 10-year median follow-up analysis is planned for 2014. For the 77 deceased patients, the causes of death were: lymphoma (n = 57; 74%), toxicity (n = 7; 9%), second malignancy (n = 2; 3%), other causes (n = 6; 8%), and unknown (n = 5; 6%).

The 3- and 5-year OS for the ITTP were 56% (95% CI, 48% to 63%) and 51% (95% CI, 43% to 59%), respectively (Fig 2A). The corresponding PFS were 48% (95% CI, 40% to 56%) and 44% (95% CI, 36% to 52%), respectively (Fig 2B). TTF was 41% (95% CI, 33% to 49%) and 37% (95% CI, 29% to 44%) at 3 and 5 years, respectively.

Subtype-specific analysis revealed the highest OS and PFS occurring in patients with ALCL (5 years: OS, 70%; PFS, 61%). AILT and PTCL-NOS had an OS at 5 years of 52% and 47% and PFS of 49% and 38%, respectively. The 5-year OS and PFS values for EATL (n = 21) were 48% and 38%, respectively. OS and PFS for the four major histologic PTCL subtypes are shown in Figures 2C and 2D. The differences between the four groups were not statistically significant (OS, log-rank $P = .21$; PFS, log-rank $P = .27$). However, comparing ALCL with all nonanaplastic patient cases taken as one group, the former histology had a significantly better OS ($P = .03$) and PFS ($P = .04$). Because of the low number of the more rare subtypes, only 3-year OS for the combined group of those with panniculitis-like (n = 6), T/NK nasal-type (n = 5), and hepatosplenic T-cell lymphoma (n = 5) was estimated and found to be 44%. The 5-year OS for patients who did not undergo transplantation (n = 45) was 28%, compared with 61% for the cohort receiving transplant (n = 115).

In line with protocol recommendations, elderly patients (age 61 to 67 years) received an induction treatment consisting of biweekly CHOP (ie, without etoposide; n = 42). When evaluated

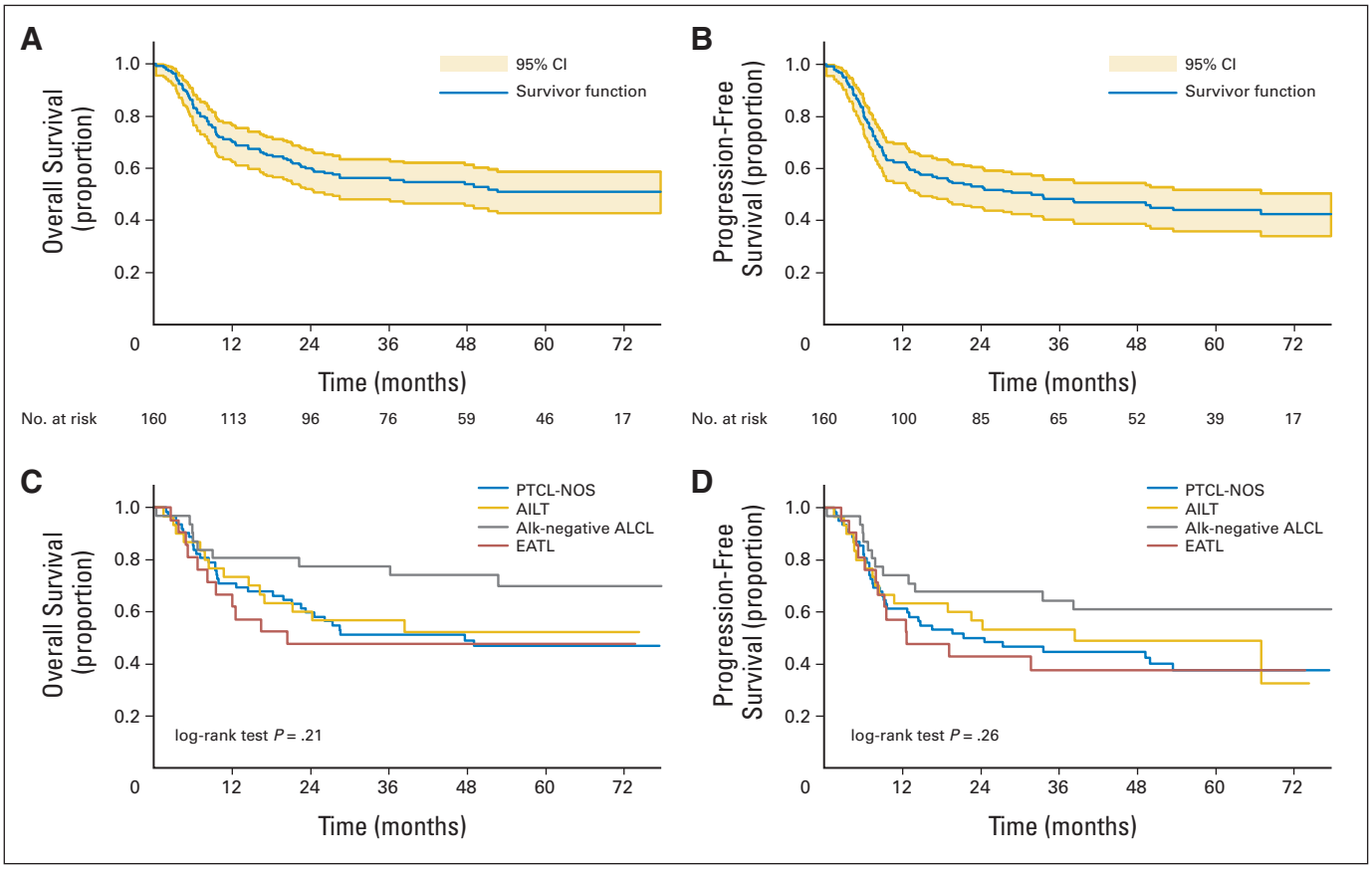

Fig 2. Kaplan-Meier estimates of (A) overall (OS) and (B) progression-free survival (PFS) for the entire NLG-T-01 cohort and (C) OS and (D) PFS for the four largest histologic subtypes. PTCL-NOS, peripheral T cell lymphoma, not otherwise specified; Alk-negative ALCL, anaplastic lymphoma kinase–negative anaplastic large cell lymphoma; AILT, angioimmunoblastic lymphoma; EATL, enteropathy-associated T cell lymphoma.

separately, this subcohort had a median age of 64 years, with four patients belonging to the low-risk, 10 to the low-intermediate, 11 to the intermediate-high, and 17 to the high-risk IPI groups. The ORR was 88% (CR/CRu, 55%; PR, 33%). The 5-year OS and PFS values for this subcohort were 45% and 34%, respectively. The corresponding values for CHOEP-treated patients age 55 to 60 years (n = 50) were similar (ie, ORR, 84% [CR/CRu, 50%; PR, 34%]; 5-year OS and PFS, 40% and 39%, respectively).

Analysis of Prognostic Parameters

When the study population was analyzed as one cohort, a significant correlation was found between IPI subgroups (low/low intermediate *v* intermediate high/high) and outcome (OS, $P = .047$; PFS, $P = .029$). If applied separately to each of the three major nodal subtypes, IPI had a predictive value for OS in AILT ($P = .02$) and for PFS in both AILT ($P = .02$) and PTCL-NOS ($P = .03$). No prognostic impact of the IPI in ALCL was observed. Considering individual clinicopathologic features, those significantly affecting OS and/or PFS at both univariate and multivariate levels were: female sex and ALCL histology associated with favorable outcome; age, BM involvement, and PS ≥ 2 as adverse prognosticators (Table 2). Analyzed as a continuous variable, increasing age was associated with a 2.9% increment of hazard ratio per year in PTCL-NOS. Female sex predicted a favorable outcome for the whole study cohort and for the nodal subtypes (PTCL-NOS, AILT, and ALCL), if analyzed as one group. At multivariate level, BM involvement at diagnosis correlated with poorer PFS but not OS. ALCL histology was an independent favorable prognosticator (OS and PFS). In the multivariate analysis, it weakened the impact of female sex. There was no significant difference between patients with ALCL and those without in terms of age, clinical stage, PS, BM involvement, and IPI score.

Reassessment of Histopathologic Diagnoses by National Reference Pathologists

Table 3 summarizes the results of the histopathologic re-review. In 139 patient cases (87%), there was agreement between the referral center and the national reference pathologist. The remaining 21 patient cases were reviewed as belonging to either another PTCL subtype (n = 13) or a non-PTCL histology (n = 8; [Hodgkin's lymphoma, n = 2; T-cell rich B-cell lymphoma, n = 3; reactive lesion, n = 2; and adult T-cell lymphoma/leukemia, n = 1]). Exclusion of these eight patients did not change 3- or 5-year OS or PFS values significantly.

DISCUSSION

The present results derive from an up-front HDT/ASCT trial with a large patient cohort, considering the rarity of the disease, and a long

Table 2. Univariate and Multivariate Cox Regression Analyses of Prognostic Clinicopathologic Parameters (all subtypes; n = 160)

Parameter	OS			PFS		
	HR	95% CI	*P*	HR	95% CI	*P*
Univariate analysis						
Age (per year)*	1.03	1.01 to 1.05	.017	1.03	1.01 to 1.05	.012
Female sex	0.54	0.32 to 0.92	.023	0.58	0.36 to 0.94	.027
BM involvement	1.72	1.07 to 2.76	.025	1.83	1.18 to 2.84	.007
ALK-negative ALCL histology	0.46	0.23 to 0.92	.029	0.54	0.29 to 0.99	.048
PS ≥ 2†	1.58	0.98 to 2.54	.058	1.59	1.02 to 2.47	.039
Elevated sLDH	1.31	0.82 to 2.10	NS	1.23	0.80 to 1.90	NS
Clinical stage III to IV	0.85	0.49 to 1.47	NS	1.09	0.63 to 1.87	NS
Multivariate analysis						
ALK-negative ALCL histology	0.46	0.23 to 0.93	.031	0.51	0.27 to 0.94	.030
Age (per year)*	1.03	1.00 to 1.05	.041	1.03	1.00 to 1.05	.028
PS ≥ 2†	1.66	1.02 to 2.71	.041	1.69	1.08 to 2.67	.023
Female sex	0.61	0.36 to 1.04	.069	0.63	0.39 to 1.03	.064
BM involvement	1.50	0.92 to 2.44	.102	1.67	1.06 to 2.63	.027

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; BM, bone marrow; HR, hazard ratio; NS, not significant; OS, overall survival; PFS, progression-free survival; PS, performance score; sLDH, serum lactate dehydrogenase.
*Analyzed as continuous variable.
†According to WHO scale 0 to 4.

median follow-up. Although a degree of patient selection will always be present in a transplantation study because of age and/or comorbidity criteria, the high median age (57 years) and adverse risk profile of the NLG-T-01 patient population indicate a low selection bias. The OS and PFS values of the present study are higher than those of a German trial,[12] in which more pretransplantation failures (34% *v* 26%) were reported. The less dose-dense induction schedule (ie, CHOP once every 3 weeks, as compared with biweekly CHOEP/CHOP) and the different conditioning regimen (total-body irradiation plus cyclophosphamide, as compared with BEAM/BEAC) may explain the better outcome seen in the NLG-T-01 study. A recent retrospective analysis of patients with PTCL treated within German high-grade non-Hodgkin's lymphoma trials suggested a beneficial impact of etoposide.[17] However, the advantage was only found for event-free survival, not OS, and it was primarily in patients with ALK-positive ALCL and/or low-risk IPI. These features are either absent (ALK-positive disease) or scarcely represented (low-risk IPI) in the present study. In fact, when comparing the outcome of those patients age 61 to 67 years, who in our study received biweekly CHOP as induction regimen, with that of patients age 55 to 60 years treated with CHOEP, 5-year OS and PFS were similar.

Table 3. Reassessment of Referral Center–Based Histopathologic Diagnoses by National Reference Hematopathologists

Subtype (ITT population)	RE-REV by National Pathologists								
	PTCL-NOS	AILT	ALK-Negative ALCL	EATL	T/NK Nasal Type	HSL	PL	Not PTCL	Total ITT
PTCL-NOS	54	3	0	1	0	0	0	4	62
AILT	3	26	0	0	0	0	0	1	30
ALK-negative ALCL	3	0	26	1	0	0	0	1	31
EATL	1	0	0	20	0	0	0	0	21
T/NK	0	0	0	0	4	0	0	1	5
HSL	1	0	0	0	0	3	0	1	5
PL	0	0	0	0	0	0	6	0	6
Total RE-REV	62	29	26	22	4	3	6	8	160

Abbreviations: AILT, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; EATL, enteropathy-associated T-cell lymphoma; HSL, hepatosplenic T-cell lymphoma; ITT, intention to treat; PL, panniculitis like; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; RE-REV, re-review; T/NK, T cell/natural killer.

In the present study, ALK-negative ALCL histology showed a better outcome, as compared with other subtypes. A similar observation was recently reported by the International T-Cell Project,[18] whereas in a retrospective study from the HOVON (Hemato-Oncologie voor Volwassenen Nederland) group, outcome results for patients with ALK-negative ALCL were similar to those of patients with PTCL-NOS.[19] We found the IPI to prognosticate effectively in AILT and PTCL-NOS but not in ALK-negative ALCL. Unlike the findings from the International T-Cell Project, in which IPI significantly predicted outcome in ALK-negative ALCL,[18] our finding is more in line with a recent report from the GELA (Groupe d'Etude des Lymphomes de l'Adulte) group, in which only age > 40 years and high β_2 microglobulin were adverse outcome predictors in ALK-negative ALCL.[20] These differences may be explained by an equalizing impact produced by the more intensive and homogeneous therapeutic background of the patient cohorts in both the NLG-T-01 and GELA experiences, as compared with the archival data from the International T-Cell Project analysis. In the NLG-T-01 study, age was an important prognostic parameter (hazard ratio increase of 3% per year of age). However, probably because of the limited numbers, a significantly adverse impact of increasing age was only detected in the largest subtype (ie, PTCL-NOS). A favorable prognostic factor was female sex. This parameter had prognostic significance for the entire study cohort as well as for the nodal subtypes (PTCL-NOS, AILT, and ALCL), if analyzed as one group. The latter finding probably reflects the exclusion of the predominantly male sex–associated[1] and prognostically unfavorable[21,22] extranodal subtypes. An adverse impact of male sex on outcome has also been reported for aggressive B-cell lymphomas.[23,24]

The NLG-T-01 trial was designed to include an additional histopathologic reassessment by national reference pathologists of the diagnoses established at referral center level and on which treatment decisions were made. This additional review changed the diagnosis in eight patient cases (5%) to non-PTCL and in 13 (8%) to another PTCL subtype. This highlights the diagnostic difficulties often encountered in PTCL, even by experienced hematopathologists, and underscores the importance of a highly specialized diagnostic approach.

The present analysis is based on a robust median follow-up (60.5 months), which is the longest, to our knowledge, among recently reported major prospective PTCL trials (median follow-up lengths between 18 and 33 months).[9,25,26] This circumstance allowed us to evaluate the occurrence of treatment failures over time. Approximately one fourth of patients (26%) experienced treatment failure before transplantation. This group included patients with truly refractory disease, for whom a better response could only be achieved through an improved induction schedule. The anti-CD52 antibody

alemtuzumab has been added to CHOP/CHOP-like chemotherapy as first-line PTCL treatment in different phase II trials[27,28] and is currently being tested in an ongoing international randomized trial (ACT [Alemtuzumab and CHOP in T-Cell Lymphoma] trial; clinicaltrials.gov identifier: NCT00646854). Other new drugs such as antifolates,[25] histone deacetylase inhibitors,[26] interleukin-2–toxin conjugates,[29] and antibody-drug conjugates[30] have shown promising efficacy in relapsed/refractory PTCL and are close to phase III trial testing in the first-line setting.

Another fraction of the patients (18%) in the NLG-T-01 study progressed/relapsed within the first 2 years after transplantation. Although initially chemosensitive, these patients probably retained therapy-resistant residual disease responsible for early post-transplantation relapse. An improved consolidation strategy such as allogeneic BM transplantation may be of benefit.[31] However, for the latter modality, toxicity is still a concern. Also, a mere change in consolidation strategy without induction improvement would still leave the problem of primary refractory disease unsolved.

A minor fraction of the patients (7%) included in the NLG-T-01 study relapsed more than 2 years after transplantation. This may provide a rationale, at least in some patients, for maintenance therapy. Oral compounds such as the antiangiogenic drug lenalidomide, the mammalian target of rapamycin inhibitor everolimus, and aurora kinase inhibitors have shown promising results in vivo[32,33] and in vitro.[34]

In conclusion, the NLG-T-01 study has shown that a dose-dense induction treatment followed by HDT/ASCT is well tolerated and leads to long-term PFS in 44% of patients with treatment-naive systemic PTCL. This represents an encouraging outcome, particularly considering the high median age and adverse risk profile of the present study population. Therefore, on the basis of these results, dose-dense induction and HDT/ASCT should be considered a rational choice for the first-line treatment of transplantation-eligible patients with PTCL. Moreover, the present results represent a useful comparative reference platform for the evaluation of new treatment strategies in PTCL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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