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ORIGINAL ARTICLE

A retrospective study of the CHOP, CHOPE, and CHOPE/G regimens as the first-line treatment of peripheral T-cell lymphomas

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Abstract

Purpose The standard treatment for peripheral T-cell lymphomas (PTCLs) is undetermined. We designed a CHOPE/G regimen (cyclophosphamide, pirarubicin, vincristine, prednisolone, and etoposide alternating with a gemcitabine-based regimen) as the first-line treatment of PTCLs and compared with CHOP (cyclophosphamide, pirarubicin, vincristine, and prednisolone) and CHOPE (CHOP plus etoposide) regimen to evaluate the optimal chemotherapy regimen.

Methods 116 previously untreated PTCL patients received CHOP ($N=46$), CHOPE ($N=46$), or CHOPE/G ($N=24$) regimen at Peking University Cancer Hospital from 2009 to 2017 and were retrospectively analyzed.

Results The overall response rates (ORRs) of the CHOP, CHOPE, and CHOPE/G groups were 82.6%, 76.1%, and 75.0% ($p=0.673$), with complete response (CR) rates of 32.6%, 56.5%, and 45.7% ($p=0.063$), respectively. Within a median follow-up time of 35.5 months, the 3-year overall survival (OS) rates of the CHOP, CHOPE, and CHOPE/G groups were 37.0%, 47.0%, and 56.3% ($p=0.107$), and the 3-year progression-free survival (PFS) rates were 19.9%, 29.9%, and 5.3% ($p=0.093$), respectively. Compared with the CHOP regimen alone, CHOPE had a significantly higher CR rate ($p=0.021$) with more favorable OS ($p=0.046$). The CHOPE/G regimen did not improve the ORR, CR rate, or OS compared with either the CHOP or CHOPE, with a significantly poorer PFS compared with the CHOPE regimen ($p=0.029$). Anemia and thrombocytopenia occurred most frequently in the CHOPE/G group (anemia 83.3%, $p=0.035$; thrombocytopenia 50%, $p=0.015$).

Conclusions Compared with CHOP alone, CHOPE regimen improved the efficacy and survival; while the addition of gemcitabine in the front-line therapy resulted in more adverse events without benefit of survival.

Keywords Peripheral T-cell lymphomas · Chemotherapy · CHOP · Etoposide · Gemcitabine

Introduction

Lymphoma is a group of malignancies derived from the hematopoietic and lymphoid systems. Approximately 90% of lymphomas are non-Hodgkin lymphoma (NHL) [1]. Peripheral T-cell lymphomas (PTCLs) are an uncommon heterogeneous group of NHLs. The incidence of PTCL varies geographically. PTCLs account for 5–10% of NHLs in Western countries compared to 22–32.5% in East Asia and above 30% in China [2–5]. According to the 2016 revision of the World Health Organization classification of lymphoid neoplasms [6], more than 20 subtypes of mature T-cell and natural killer (NK) neoplasms are defined. According to an international multicenter retrospective study [7], the most common histological subtype of mature T/NK T-cell lymphoma was PTCL not otherwise specified (NOS) (25.9%), followed by angioimmunoblastic T-cell lymphoma (AITL), natural killer/T-cell lymphoma (NKTCL), primary cutaneous anaplastic large-cell lymphoma (ALCL), adult T-cell leukemia/lymphoma, ALK-positive anaplastic large-cell lymphoma (ALK^+ALCL), and ALK-negative anaplastic large-cell lymphoma (ALK^-ALCL). Enteropathy-associated T-cell lymphoma (EATL) and subcutaneous panniculitis-like lymphoma are rare and account for less than 5% of T/NK T-cell lymphomas [7].

Because of the aggressive biological characteristics of the tumor, drug resistance and patients' poor baseline condition,

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PTCLs show poor response to treatment. Even for patients with complete or partially relieved disease, the high recurrence rate still demonstrates the failure of treatment. For the low incidence of PTCLs, evidences of treatment mainly drive from retrospective trails and the standard initial treatment has not been established. According to the National Comprehensive Cancer Network (NCCN) guidelines for T-cell lymphoma [8], version 2018, clinical trials and multiagent chemotherapy are recommended for PTCL patients, except ALK-positive ALCL and NT/T-cell lymphoma. Standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens are most widely used for PTCL patients, but the treatment outcomes are generally unfavorable. According to a real-world study [9], the overall response rate (ORR), 5-year overall survival (OS), and 5-year progression-free survival (PFS) of patients with PTCL who received the CHOP regimen were 65%, 30%, and 23%, respectively. Unfortunately, there is a lack of evidence regarding regimens that are superior to CHOP. Some studies have indicated that the addition of etoposide to the CHOP regimen (CHOPE) may be more favorable and have a higher complete response (CR) rate, ORR, or event-free survival (EFS) rate in PTCL patients except for those with ALK^+ALCL [9–11]; however, no significant improvement in OS was observed. Other intensifications of chemotherapy regimens, such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and prednisone) and dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), have not been generally proved successful [12, 13]. In spite of this, many studies have indicated that gemcitabine-based regimens are feasible and show encouraging activity in PTCL patients [14–18], but there is a lack of randomized controlled trials with large samples.

To determine the potential advantage of the combination of etoposide and gemcitabine with an anthracycline-based regimen, inspired by previous studies, we designed a CHOPE alternating with a gemcitabine-based regimen (CHOPE/G). Here, we retrospectively compared the efficiency, safety, and outcome of the CHOP, CHOPE, and CHOPE/G regimens as the initial treatment in PTCL patients. The clinical experience of our study may provide references for future research.

Materials and methods

Patients

From 2009 to 2017, 116 previously untreated PTCL patients were admitted to Peking University Cancer Hospital and received initial chemotherapy. We retrospectively reviewed their clinical characteristics, treatment efficacy, and outcome. The histological subtypes of the 116 cases were AITL, ALK^-ALCL, PTCL NOS, EATL, subcutaneous panniculitis-like T-cell lymphoma, and hepatosplenic γδT-cell lymphoma. For the clinical characteristics, treatment strategy and outcomes significantly varied from other PTCL subtypes; NKTCL, cutaneous ALCL, and ALK^+ALCL were not included. None of the 116 patients received autologous hematopoietic stem-cell transplantation (AHSCT) as first-line therapy. The pathological diagnosis of all patients was identified by the pathology department of Peking University Cancer Hospital according to "the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues" [19]. The disease stage was defined according to the Ann Arbor staging system. A bone marrow biopsy was performed on all patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Chemotherapy

All 116 patients received chemotherapy as the initial therapy. A total of 46 (39.7%) patients received a CHOP regimen [cyclophosphamide 750 mg/m^2 intravenously on day 1, pirarubicin 50 mg/m^2 intravenously on day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) intravenously on day 1, and prednisolone 100 mg/day peroral on days 1–5]; 46 (39.7%) patients received a CHOPE regimen [cyclophosphamide 750 mg/m^2 intravenously on day 1, pirarubicin 50 mg/m^2 intravenously on day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) intravenously on day 1, etoposide 60 mg/m^2 intravenously on days 1–3, and prednisolone 100 mg/day peroral on days 1–5]; and 24 (20.7%) patients received a CHOPE/G regimen [CHOPE alternating with a GemOx regimen (gemcitabine 1000 mg/m^2 intravenously on day 1 and oxaliplatin 100 mg/m^2 intravenously on day 1) or GDP regimen (gemcitabine 1000 mg/m^2 intravenously on days 1 and 8, cisplatin 25 mg/m^2 intravenously on days 1–3, and dexamethasone 10 mg/day intravenously on days 1–4)]. Each cycle of CHOP, CHOPE, and GDP was administered every 21 days, and the cycle of the GemOx regimen was 14 days.

Efficacy assessment and follow-up criteria

The response to treatment was assessed after every two cycles of chemotherapy. The assessment of treatment response was based on the 2014 Lugano classification and adopted retrospectively for cases before 2014 [20]. The ORR was defined as the rate of CR plus partial response (PR). All patients were followed up until August 2018 using the medical records of our institute or by telephone. OS was defined as the time from diagnosis to death for any reason

or the most recent follow-up. PFS was defined as the time from diagnosis to disease progression, death for any reason, or the most recent follow-up.

Statistical analysis

All data were analyzed by IBM SPSS Statistics, version 22.0 (SPSS, Chicago, IL). Differences between clinical characteristics and response were analyzed with the χ^2 test or one-way analysis of variance. Survival functions were estimated by the Kaplan–Meier method, and differences between groups were compared by log-rank test. A $p < 0.05$ was regarded as statistically significant, and all p values were two-sided.

Results

Patient characteristics

Of the 116 patients, 83 (71.6%) were male, and 33 (28.4%) were female. The median age was 57.5 years old (years range 14–85); 61 (52.5%) patients were over 60 years old. The median onset time to diagnosis was 3.5 months. Six (5.2%) patients had a score > 1 on the Eastern Cooperative Oncology Group (ECOG) performance status. The histological subtypes of these 116 PTCL patients included 57 (49.1%) AITLs, 25 (21.6%) ALK$^-$ALCLs, 25 (21.6%) PTCL NOS, and 9 other subtypes (6 EATL, 2 hepatosplenic γδT-cell lymphoma and 1 subcutaneous panniculitis-like T-cell lymphoma). At the time of diagnosis, 26 (22.4%) patients were at stage I/II, 90 (77.6%) patients were at stage III/IV, and 43 (37.1%) patients had B symptoms. No significant difference in age and B symptoms was found among the different histology subgroups. Advanced stage (stage III or IV) was significantly more common in patients with AITL (54/57, 94.7%) than patients with other histological subtypes ($p < 0.001$). The clinical characteristics and distribution of the different chemotherapy regimens are shown in Table 1. Except for age, the basic characteristics of the three chemotherapy regimen groups showed no significant difference.

Table 1 Histological subtypes and clinical characteristics of the entire cohort ($N = 116$)

Clinical characteristics	ALL patients ($N = 116$)	CHOP ($N = 46$, 39.7%)	CHOPE ($N = 46$, 39.7%)	CHOPE/G ($N = 24$, 20.7%)	p value
Gender					0.470
Male	83 (71.6%)	30 (65.2%)	35 (76.1%)	18 (75.0%)	
Female	33 (28.4%)	16 (34.8%)	11 (23.9%)	6 (25.0%)	
Ratio of male/female					
Age					0.000
Median age (years)	57.5	66.37	50.07	54.75	
Years range	14–85	14–85	15–67	28–70	
Age > 60 years	61 (52.5%)	36 (78.3%)	16 (34.8%)	9 (37.5%)	
ECOG score > 1	6 (5.2%)	4 (8.7%)	1 (2.2%)	1 (4.2%)	0.358
B symptoms	43 (37.1%)	21 (45.7%)	11 (23.9%)	11 (45.8%)	0.059
Histological subtype					0.075
AITL	57 (49.1%)	21 (45.7%)	23 (50.0%)	13 (54.2%)	
ALK$^-$ALCL	25 (21.6%)	10 (21.7%)	11 (23.9%)	4 (16.7%)	
PTCL NOS	25 (21.6%)	7 (15.2%)	11 (23.9%)	7 (29.2%)	
Others	9 (7.8%)	8 (17.4%)	1 (2.2%)	0 (0%)	
Stage III–IV	90 (77.6%)	33 (71.7%)	36 (78.3%)	21 (87.5%)	0.321
Extranodal involvement > 1	27 (23.3%)	12 (28.3%)	10 (21.7%)	4 (16.7%)	0.525
BM involvement	10 (8.6%)	4 (8.7%)	2 (4.3%)	4 (16.7%)	0.219
LDH > 240 IU/L	54 (46.6%)	22 (47.8%)	19 (41.3%)	13 (54.2%)	0.577
IPI score					0.085
IPI 0–1	37 (31.9%)	11 (23.9%)	20 (43.5%)	6 (25.0%)	
IPI 2	38 (32.8%)	12 (26.1%)	16 (34.8%)	10 (41.7%)	
IPI 3	29 (25.0%)	16 (34.8%)	6 (13.0%)	7 (29.2%)	
IPI 4–5	12 (10.3%)	7 (15.2%)	4 (8.7%)	1 (4.2%)	
Mean chemotherapy cycles	5.2	5	5.3	5.4	0.735

ECOG Eastern Cooperative Oncology Group, *BM* bone marrow, *LDH* lactate dehydrogenase, *IPI* International Prognostic Index

Table 2 Response to initial treatments of all PTCLs

Regimen	Response					
	ORR	CR rate	CR	PR	SD	PD
CHOP ($N=46$)	82.6%	32.6%	15	23	3	5
CHOPE ($N=46$)	76.1%	56.5%	26	9	2	9
CHOPE/G ($N=24$)	75.0%	50.0%	12	6	1	5
ALL patients ($N=116$)	78.4%	45.7%	53	38	6	19
p value	0.673	0.063				

ORR overall response rate, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 3 Response and survival of different initial chemotherapy regimens

Regimen	ORR	CR rate	3-year OS	3-year PFS
CHOP ($N=46$)	82.6%	32.6%	37.0%	19.9%
CHOPE ($N=46$)	76.1%	56.5%	47.0%	29.9%
p value	0.440	0.021	0.046	0.165
CHOP ($N=46$)	82.6%	32.6%	37.0%	19.9%
CHOPE/G ($N=24$)	75.0%	50.0%	56.3%	5.3%
p value	0.450	0.156	0.386	0.344
CHOPE ($N=46$)	76.1%	56.5%	47.0%	29.9%
CHOPE/G ($N=24$)	75.0%	50.0%	56.3%	5.3%
p value	1.000	0.603	0.847	0.029

ORR overall response rate, *CR* complete response, *OS* overall survival, *PFS* progression-free survival

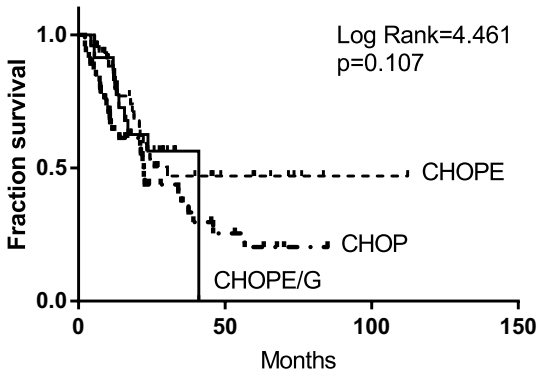

Fig. 1 Overall survival of different initial chemotherapy regimens

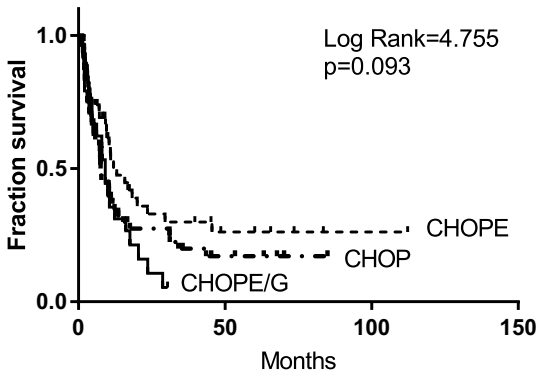

Fig. 2 Progression-free survival of different initial chemotherapy regimens

Treatment and response

In this study, 1–8 cycles of chemotherapy (median 6) were administered to all 116 cases as the initial treatment. Forty-six (39.7%) patients received the CHOP regimen, 46 (39.7%) patients received the CHOPE regimen, and 24 (20.7%) patients received the CHOPE/G regimen. Evaluation of response was available for all 116 patients and is listed in Table 2. The overall ORR and CR rates were 78.4% and 45.7%, respectively. The ORRs of the CHOP, CHOPE, and CHOPE/G groups were 82.6%, 76.1%, and 75.0% ($p=0.673$), with CR rates of 32.6%, 56.5%, and 45.7%, respectively ($p=0.063$). Comparisons of the chemotherapy regimens against each other are shown in Table 3. The ORR and CR rates showed no significant difference between the CHOPE/G and CHOP regimens or the CHOPE/G and CHOPE regimens. Although the ORR showed no significant difference, the CR rate of the CHOPE regimen group was significantly higher than that of the CHOP regimen group (56.5% vs. 32.6%, $p=0.021$).

Survival and outcome

Within a median follow-up time of 35.5 months, the estimated 3-year OS rate and 3-year PFS rate were 43.6% and 20.6%, respectively. The median OS and median PFS were 24.4 months and 10.2 months, respectively. The OS and PFS of the different chemotherapy regimen groups are shown in Table 3 and Figs. 1 and 2. The 3-year OS rates of the CHOP, CHOPE, and CHOPE/G regimen groups were 37.0%, 47.0%, and 56.3%, respectively ($p=0.107$; CHOP vs. CHOPE,

$p = 0.046$; CHOP vs. CHOPE/G, $p = 0.386$; CHOPE vs. CHOPE/G, $p = 0.874$). The 3-year PFS rates of the CHOP, CHOPE, and CHOPE/G regimen groups were 19.9%, 29.9%, and 5.3%, respectively ($p = 0.093$; CHOP vs. CHOPE, $p = 0.165$; CHOP vs. CHOPE/G, $p = 0.344$; CHOPE vs. CHOPE/G, $p = 0.029$). The CHOPE regimen showed a better OS than CHOP and a better PFS than CHOPE/G.

To determine the difference in response to the three chemotherapy regimens among the different pathological subtypes, subgroup analysis was performed. For patients with ALK^-ALCL, the CHOPE regimen group had the highest ORR (90.9%, $p = 0.129$) and CR rate (81.8%, $p = 0.134$) and the most favorable survival (3-year PFS 79.5%, $p = 0.058$; 3-year OS 100%, $p = 0.004$). Except of that, no significant difference was found between the three chemotherapy regimens among different pathological subtypes. Furthermore, a subgroup comparison of the ORR, CR rate, PFS, and OS of the CHOP, CHOPE, and CHOPE/G regimens between the International Prognostic Index (IPI) < 2 and IPI ≥ 2 groups was also performed. No significant difference was observed between the three chemotherapy regimens in the groups with different IPI scores.

Safety and tolerability

Common adverse events are listed in Table 4. Adverse events were mainly hematological toxicity, such as leukopenia, anemia, and thrombocytopenia. The CHOPE/G regimen group had a higher incidence of anemia and thrombocytopenia than the CHOP and CHOPE groups ($p < 0.05$). No treatment-related deaths occurred in this study.

Discussion

PTCL is a rare subgroup of NHLs with high heterogeneity and poor outcomes. According to some retrospective studies, the median onset age of PTCL was 50–65 years, with a male predominance; over 50% of patients were at an advanced stage, and over 30% of patients had B symptoms [9, 10, 21, 22]. In this study, the median age of 116 PTCL patients was 57.5 years; 71.6% of patients were male; and advanced-stage disease and B symptoms were present in 77.6% and 37.1% of patients, respectively, which was in accordance with a previous study. The clinical characteristics of PTCL patients differ by histological subtype. In our study, advanced stage and B symptoms were more frequently observed in patients with AITL, also in accordance with some retrospective studies [10, 21].

In contrast to the treatment of B-cell lymphoma, standard first-line treatment of PTCL remains controversial. CHOP-based regimens are prescribed to a large majority of patients but cannot achieve satisfactory efficacy other than in ALK^+ALCL patients. Some studies have shown a possible small improvement by adding etoposide to the standard CHOP regimen (CHOPE). According to a retrospective study of the German high-grade NHL study group [10], younger PTCL (without ALK^+ALCL) patients (< 60 years old) benefited more from the CHOPE regimen than patients with CHOP, with significant EFS improvement (75.4% vs. 51%, $p = 0.003$) but no OS improvement observed. A real-world study of the Swedish Lymphoma Registry showed that PTCL patients treated with the CHOPE regimen exhibited a trend toward a higher ORR than did CHOP patients (81% vs 70%, $p = 0.052$), but CHOPE was not associated with better OS or PFS [9]. In this study, we compared the efficacy of the CHOP and CHOPE regimens as first-line treatment for PTCL. The CHOPE regimen showed a significantly higher CR rate than the CHOP regimen, with an improvement in

Table 4 Most common adverse events

Adverse events	Regimen							
	All adverse events				Grade 3–4 adverse events			
	CHOP ($N = 46$)	CHOPE ($N = 46$)	CHOPE/G ($N = 24$)	p value	CHOP ($N = 46$)	CHOPE ($N = 46$)	CHOPE/G ($N = 24$)	p value
Leukopenia	38 (82.6%)	36 (78.3%)	30 (83.3%)	0.824	17 (37.0%)	23 (50.0%)	11 (45.8%)	0.442
Neutropenia	36 (78.3%)	35 (76.1%)	18 (75.0%)	0.946	16 (34.8%)	23 (50.0%)	11 (45.8%)	0.332
Anemia	25 (54.3%)	25 (54.3%)	20 (83.3%)	0.035	5 (10.9%)	3 (6.5%)	6 (25.0%)	0.075
Thrombocytopenia	10 (21.7%)	9 (19.6%)	12 (50.0%)	0.015	4 (8.7%)	3 (6.5%)	7 (29.2%)	0.015
Transaminase elevation	8 (17.4%)	13 (28.3%)	2 (12.5%)	0.235	1 (2.2%)	1 (2.2%)	0 (0%)	0.767

All adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

OS. For ALK⁻ALCL patients in particular, the CHOPE regimen exhibited a significantly favorable OS (3-year OS 100%). However, it is noteworthy that the median age of the CHOP group in our study was older than that of the CHOPE group, which may have caused bias between the treatment groups.

Recognizing the inadequacies of the CHOP-like regimen, non-anthracycline-based regimens have been explored for the treatment of PTCLs. Zinzani et al. [14] reported that gemcitabine, as a single agent in treating peripheral T-cell lymphoma unspecified (PTCLU), had a CR rate of 20% and an ORR of 55%. In a retrospective study [20], 26 PTCL patients received a gemcitabine-based combination regimen, and the CR rate, ORR, 2-year OS, and 2-year PFS were 46.2%, 88.5%, 63.7%, and 45.9%, respectively. According to a phase 2 trial held by the Southwest Oncology Group [23], the PEGS (cisplatin, etoposide, gemcitabine, and methylprednisolone) regimen was given to 34 newly diagnosed PTCL patients (excluding ALK⁺ALCL), and the ORR, 2-year PFS, and 2-year OS were 39%, 12%, and 30%, respectively. A phase 2, international multicenter trial [24] randomly assigned 43 PTCL patients to CHOP and 44 to GEM-P (gemcitabine, cisplatin, and methylprednisolone). The CR rate, PFS, and OS of the GEM-P group were not significantly inferior compared with those of the CHOP group, and the trial was closed early (CR rate GEM-P vs. CHOP: 46% vs. 62%, $p=0.164$; 2-year PFS GEM-P vs. CHOP: 38% vs. 36.6%, $p=0.82$; 2-year OS GEM-P vs. CHOP: 63.9% vs. 51.0%, $p=0.300$). In our study, we first applied the CHOPE alternating with a gemcitabine-based regimen (CHOPE/G) to treat PTCL. Unfortunately, the CHOPE/G regimen did not improve the CR rate or ORR compared with the CHOP or CHOPE regimen. The 3-year OS of CHOPE/G showed no significant difference compared with that of CHOP and CHOPE. However, the CHOPE/G regimen showed a significantly poorer PFS than the CHOPE regimen (3-year PFS 5.3% vs. 29.9%, $p=0.029$). In the subgroup analysis according to histological subtype or IPI score, CHOPE/G did not show any significant superiority either. Furthermore, the CHOPE/G group experienced significantly more adverse events related to anemia and thrombocytopenia than the two other groups. Therefore, the CHOPE/G regimen is not recommended as the first-line therapy of PTCLs. The CHOP or CHOPE regimen may remain the basis of PTCL therapy.

In conclusion, the CHOPE/G regimen we proposed was unsatisfactory for PTCLs given the lack of improvement in CR rate or ORR, the unfavorable PFS, and the occurrence of more adverse events. Anthracycline-based regimens remain optimal. The addition of etoposide to the CHOP regimen improved the CR rate and OS compared with CHOP alone for PTCLs, especially for ALK⁻ALCLs. Further prospective studies with a large sample size are needed to explore a more favorable therapy strategy for PTCL patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

Informed consent Informed consent was obtained from all individual participants included in the study.

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