REGULAR ARTICLE

blood advances

Pralatrexate injection combined with CHOP for treatment of PTCL: results from the Fol-CHOP dose-finding phase 1 trial

Swaminathan P. Iyer,[1] Patrick B. Johnston,[2] and Stefan K. Barta[3,4]

[1]Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Internal Medicine, Division of Hematology, Mayo Clinic, Rochester, MN; [3]Lymphoma Program, University of Pennsylvania School of Medicine. Philadelphia, PA; and [4]Fox Chase Cancer Center, Philadelphia, PA

Key Points

- Pralatrexate in combination with CHOP (Fol-CHOP) demonstrated clinically meaningful efficacy (ORR, 83.9%) in newly diagnosed PTCL.
- Fol-CHOP was reasonably well tolerated, and toxicities were clinically acceptable and manageable.

Pralatrexate is a folate antagonist that selectively enters cells expressing reduced folate carrier type 1 and competitively inhibits dihydrofolate reductase, leading to interruption of RNA synthesis, DNA replication, and apoptosis. This phase 1 study was conducted to evaluate the maximum tolerated dose (MTD) of pralatrexate in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen (part 1) and the response and pharmacokinetics of 6 cycles of this combination (CHOP + Folotyn 30 mg/m^2 [Fol-CHOP]) in patients with newly diagnosed peripheral T-cell lymphoma (PTCL). In part 1, on days 1 and 8 of each cycle, patients were treated with 10, 15, 20, 25, or 30 mg/m^2 of pralatrexate in combination with CHOP, per dose escalation, in 5 sequential cohorts. No patients experienced DLTs in cohorts 1, 2, 3, 4, and 5. The pralatrexate dose of 30 mg/m^2 was selected to be combined with CHOP for part 2 and administered to 33 additional patients in the expansion cohort. At the MTD, the Fol-CHOP regimen was generally well tolerated in patients with PTCL, with an overall response rate (ORR) of 83.9% (20 complete response and 6 partial response), as assessed by treating investigators. Thirty-five patients (67.3%) experienced grade 3/4 treatment-emergent adverse events, the most common of which were anemia (21.2%), neutropenia (19.2%), febrile neutropenia (11.5%), fatigue, mucosal inflammation, nausea, and vomiting (7.7% each). In conclusion, Fol-CHOP was found to be a safe and effective treatment for newly diagnosed PTCL and deemed worthy of further investigation. This trial was registered at www.ClinicalTrials.gov as #NCT02594267.

Introduction

Peripheral T-cell lymphoma (PTCL) refers to a heterogeneous group of aggressive mature T-cell non-Hodgkin lymphomas accounting for 10% to 15% of all newly diagnosed non-Hodgkin lymphomas.[1,2] Of 28 distinct clinical entities, the most common subtypes of PTCL, representing two-thirds of all PTCL cases in North America, include PTCL not otherwise specified (PTCL NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). The median overall survival (OS) of PTCL is low (<2 years), with a reported 5-year survival for the most common subtypes being <50%.[2-5]

Firstline, standard of care (SOC) treatment of PTCL often comprises combination therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Despite its widespread use,

Submitted 30 June 2023; accepted 31 October 2023; prepublished online on *Blood Advances* First Edition 29 November 2023; final version published online 11 January 2024. https://doi.org/10.1182/bloodadvances.2023011095.

All data are available on request from corresponding author, Swaminathan P. Iyer (spiyer@mdanderson.org).

The full-text version of this article contains a data supplement.

CHOP has not been studied in prospective, randomized studies and was associated with a dismal 5-year OS of only 37% in a retrospective meta-analysis of 2912 patients with PTCL treated with CHOP or CHOP-like regimens.[6-8] However, no other single-agent or combination regimen has demonstrated superior efficacy to CHOP with the exception of brentuximab vedotin (BV) + cyclophosphamide, doxorubicin, and prednisone (CHP) for $CD30^+$ PTCL, and it, therefore, remains a primary choice for firstline therapy for non-ALCL PTCL. Various strategies to modify the CHOP regimen have been investigated in an effort to increase response rates and improve durability of responses, without any clear improvements to long-term efficacy being observed. Strategies have included the addition of other agents, including biologics ("CHOP + X"), more intensive dosing administration, and, for patients who reach complete remissions, high-dose chemotherapy using autologous stem cell rescue as consolidation therapy.[9-11] Allogeneic stem cell transplantation is also recognized as a feasible option for patients with PTCL who are candidates for the procedure, although significant treatment-related toxicity has been observed.[12-14] Although the reported survival outcomes remain quite poor, response rates for CHOP-based therapies have been relatively high. As an example, a recent trial comparing CHOP vs BV-CHP in $CD30^+$ PTCLs showed an overall response rate (ORR) of 72% for CHOP and complete response (CR) of 56%.[15] Overall, the available data related to PTCL treatment shows that firstline CHOP can provide an initial response for many patients; however, fewer are able to achieve CR, and even less achieve durable remissions.

Pralatrexate monotherapy has demonstrated activity in PTCL and was the first drug approved in the United States by the US Food and Drug Administration for treatment of relapsed/refractory (R/R) PTCL in 2009, based on doses of 30 mg/m^2 weekly for 6 weeks of a 7-week treatment cycle and an ORR of 29% in a heavily pretreated population.[13,16] In 2016, O'Connor et al presented the findings of their case match control analysis of 83 patients with R/R PTCL treated in the PROPEL study, compared with matched controls.[17] Despite the heavily treated PROPEL population, the median OS of pralatrexate-treated patients was significantly higher at 16.6 months than of matched controls at 4.0 months (hazard ratio, 0.426).[17] Further evidence for its activity in PTCL was provided by the phase 3 LUMIERE trial, which randomized patients to the investigative drug alisertib and SOC comparator (investigator choice of gemcitabine, romidepsin, or pralatrexate); pralatrexate was administered to 80 participants (60% of 3 possible controls) and resulted in a CR rate of 25%, highest of the drugs studied in the trial (CR for investigative drug, 18%; CR for another SOC comparator, 6%).[18]

This single-agent activity provided the rationale for adding pralatrexate to CHOP in the frontline setting. Pralatrexate and each of the components of the CHOP regimen target different aspects of tumor cell growth and proliferation through different mechanisms of action. This suggests the potential that a new combination regimen may provide for synergistic antitumor effect and have limited additive toxicities.

Herein, we describe the results of a phase 1 dose-escalating study investigating the maximum tolerated dose (MTD) of pralatrexate in combination with CHOP regimen and associated response rates in patients with newly diagnosed PTCL.

Materials and methods

Study design and oversight

This multicenter, open-label, dose-finding, dose-escalation phase 1 trial was conducted in 2 parts: the first with the primary objective to evaluate the MTD of pralatrexate in combination with CHOP and the second part with an expansion cohort of 30 patients treated at the MTD to better characterize safety and efficacy of 6 cycles of the pralatrexate-CHOP (Folotyn-CHOP [Fol-CHOP]) combination.

The study was reviewed and approved by the institutional review boards at each of the 4 participating sites and was registered at as NCT02594267. The study conduct complied with the Declaration of Helsinki and followed International Conference on Harmonization Guidelines for Good Clinical Practice. All participating patients provided written informed consent and understood that study participation was voluntary.

Selection of patients

Patients were eligible if they were aged ≥18 years with a newly diagnosed, untreated, histologically confirmed diagnosis of PTCL of any stage (I-IV) based on local pathology review and were eligible for CHOP chemotherapy. PTCL subtypes were classified based on the 2016 World Health Organization classification and included ALCL, ALK-positive status; ALCL, ALK-negative status; ATCL; enteropathy-associated T-cell lymphoma; extranodal natural killer/T-cell lymphoma, nasal type; hepatosplenic T-cell lymphoma; PTCL NOS; and subcutaneous panniculitis-like T-cell lymphoma.[19] Pathological diagnoses were made by each participating facility. Patients were required to have adequate cardiac function and acceptable hematologic, hepatic, and renal functions, as defined by an absolute neutrophil count ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, bilirubin level ≤ 1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase levels ≤ 2.5 upper limit of normal, and creatinine level ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 50 mL per minute. Patients also had to have an Eastern Cooperative Oncology Group performance status ≤ 2. Exclusion criteria included current concurrent malignancy (except nonmelanoma skin cancer or carcinoma in situ of the cervix) or life-threatening disease. Those with a history of prior malignancies or life-threatening conditions should have been disease free for ≥5 years. Patients were also excluded if they had congestive heart failure, uncontrolled hypertension, central nervous system metastases, uncontrolled intercurrent illness, or therapy with any investigational therapies within 30 days of study treatment.

Study treatment

In part 1 of this study, patients were enrolled in a traditional 3 + 3 dose-escalation scheme, starting with dose level 1, with dose escalation as shown in supplemental Table 1. Pralatrexate was administered at 10, 15, 20, 25, or 30 mg/m^2 as an IV on days 1 and 8 of a standard 21-day CHOP regimen (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 [maximum, 2 mg] on day 1 and oral prednisone 100 mg on days 1-5).

A DLT was defined as an adverse event (AE) that, because of its type, severity, or relationship to study drug, must be counted toward determining the MTD. For purposes of determining the MTD of pralatrexate (Folotyn; Acrotech Biopharma, East Windsor, NJ)

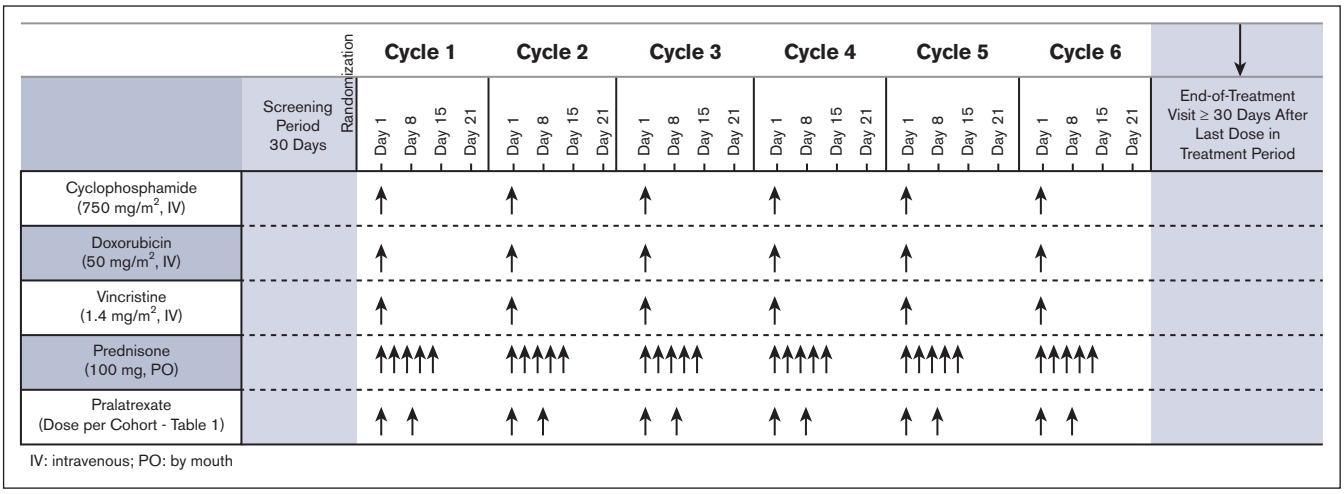

Figure 1. Part 2 treatment schedule: six 21-day cycles.

plus CHOP (Fol-CHOP) treatment, AEs that were considered DLTs when they occurred during the first treatment cycle included severe infections (grade 4); grade 4 neutropenia lasting for ≥7 days despite granulocyte colony-stimulating factor administration; any grade 4 thrombocytopenia or any grade thrombocytopenia with clinically significant bleeding (excluding epistaxis); or grade ≥3 study treatment-related nonhematologic toxicity, excluding nausea/vomiting in the absence of appropriate antiemetic therapy that occurred during the first cycle of the Fol-CHOP therapy.

Once the MTD was established in part 1, an expansion cohort (part 2) applying the MTD was included to allow for better characterization of efficacy and safety. (Figure 1) Patients were treated with the pralatrexate MTD on days 1 and 8 of each 21-day cycle, administered ~15 minutes after CHOP. Treatment was repeated every 21 days (1 cycle) for up to 6 cycles.

Patients received prophylaxis with acyclovir and sulfamethoxazole/trimethoprim during the study as well as primary prophylaxis with growth factors (filgrastim or pegfilgrastim) starting in cycle 1 (after the second dose of pralatrexate). All patients were recommended with initiate vitamin supplementation with folic acid and vitamin B12, per the currently approved label. Folic acid (1.0 mg by mouth daily) was initiated at least 10 days before pralatrexate administration. Vitamin B12 (1 mg IM) was administered within 10 weeks before the initiation of pralatrexate and was allowed to be administered during screening. Subsequent vitamin B12 injections were administered the same day as treatment with pralatrexate, and patients received vitamin B12 every 8 to 10 weeks during treatment with pralatrexate.

Patients were instructed to take leucovorin tablets (25 mg) 3 times a day for 2 days beginning 24 hours after each pralatrexate treatment as mucositis prophylaxis.[20] The next dose of pralatrexate began at least 72 hours after the last dose of leucovorin administration.

Patients participated in the study for ~26 weeks, which included a screening period (up to 30 days), up to six 3-week treatment cycles (18 weeks), and an end-of-study visit, which occurred at least 30 days after the last dose of pralatrexate.

Safety assessments

All patients who received ≥1 dose of pralatrexate were evaluable for safety, which was assessed by reported AEs, laboratory assessments, and physical examinations, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events scale, version 4.03. AEs were characterized by intensity (severity), causality, and seriousness by the investigator and recorded from the first dose of pralatrexate until at least 30 days after the last dose.

PK assessments

Pharmacokinetic (PK) studies were performed during the part 2 of the study and included collection of blood samples for PK analysis of pralatrexate for the first 12 patients at before injection, end of injection, and 0.5, 1, 3, 6, 10, 16, and 24 hours after the end of pralatrexate injection during cycle 1, dose 1.

Pralatrexate comprised a mixture of R- and S-diastereomeric folate derivatives and, as folate, has an important role in cell growth and proliferation.[21] The characterization of the plasma concentrations of pralatrexate (S-Diastereomer [PDX-10a] and R-Diastereomer [PDX-10b]) was a key secondary objective, determined using a validated LC-MS/MS bioanalytical method. PK parameters of pralatrexate (PDX-10a and PDX-10b) were calculated based on respective drug concentration–time data by a noncompartmental method using Phoenix WinNonlin (Certara, Princeton, NJ) version 8.3.1 or higher. The following PK parameters of pralatrexate (PDX-10a and PDX-10b) were estimated: area under the curve, rate of absorption, T_{max}, total clearance, $T_{1/2}$, and volume of distribution.

Efficacy assessment

Disease response was determined by investigators at each participating facility using protocol-specified integrated response criteria (Cheson classification, per the International Working Group Criteria).[22] Response evaluation recorded and reported every 2 cycles during the course of 6 cycles of Fol-CHOP (end of cycles 2, 4, and 6 and at 6, 9, and 12 months [end-of-study visit]).

The ORR was estimated by a combination of CR + partial response (PR) based on tumor scan at the end of treatment after 6

cycles of Fol-CHOP. Tumor scan performed in this study included both computed tomography and positron emission tomography–computed tomography.

Statistical analyses

The primary objectives of the study were to evaluate the MTD of pralatrexate in combination with CHOP (Fol-CHOP) for newly diagnosed patients with PTCL in part 1 of the study and evaluate the ORR after 6 cycles of Fol-CHOP in part 2. Key secondary objectives included the evaluation of progression-free survival (PFS) and safety and tolerability of Fol-CHOP as well as the characterization of PK of pralatrexate in combination with CHOP.

This study was planned to enroll 50 patients, which included a maximum of 6 patients in each cohort in part 1 until the MTD was identified and not determined by statistical power considerations. The decision to include up to 6 patients at each dose level cohort was based on the following considerations: if 1 DLT is observed among 6 patients, the estimated DLT rate is 16.7%, with a 90% confidence interval of 0.9% to 58.2%; and if 2 DLTs are observed among 6 patients, the estimated DLT rate is 33.3%, with a 90% confidence interval of 6.3% to 72.9%.

After the MTD had been identified, an additional 30 patients were planned to be treated to confirm the tolerability and assess efficacy in part 2. Estimated response rates were calculated along with corresponding 95% binomial confidence intervals.

Additional patients could be enrolled to replace unevaluable patients in cases of discontinuations unrelated to treatment-emergent AEs (TEAEs). Appropriate descriptive statistics were performed. Statistical analyses were performed using SAS version 9.4.

The extent of the patients' exposure to pralatrexate and CHOP were assessed based on 2 variables, cumulative dose received and relative dose intensity. The incidence of DLTs as well as AEs were tabulated by dose level. AEs were summarized based on the type as well as maximum grade and duration across patients for each dose level, as well as in the part 2 MTD expansion.

The populations presented for analysis included the safety analysis population, which consisted of all patients who signed informed consent, enrolled, and received at least 1 dose of the study drug, and the efficacy was assessed in the evaluable population, which included all patients who received at least 1 dose of pralatrexate and had at least 1 postbaseline tumor assessment.

Results

Patient characteristics

A total of 52 patients were screened at the 4 participating institutions between 2016 and 2018. There were no screen failures; thus, 52 patients were enrolled and 34 completed the study. Patient characteristics are shown in Table 1. In part 1, there were 4 patients enrolled at dose level 10 mg/m^2; 3 at dose levels 15 mg/m^2, 20 mg/m^2, and 25 mg/m^2 (1 each); and 6 at dose level 30 mg/m^2. Patient disposition is shown in Figure 2. Although the study planned to enroll 3 patients in cohort 1, because of a protocol deviation of a patient enrolled in cohort 5 receiving an incorrect dose of 10 mg/m^2, the dose level specified for cohort 1, the patient continued treatment and was included in the analysis of that dose level (cohort 1), and a subsequent replacement cohort 5 patient was enrolled. A summary of pralatrexate exposure, including the cumulative dose and relative dose intensity of pralatrexate, is shown in Table 2, and a summary of exposure to pralatrexate, cyclophosphamide, vincristine doxorubicin, and prednisone is shown in supplemental Table 3.

At the time of initial diagnosis using the 2016 World Health Organization criteria, the majority of patients (n = 34 [65.4%]) had PTCL NOS, 9 (17.3%) had AITL; 7 (13.5%) had ALCL, ALK-negative status; 1 (1.9%) had ALCL, ALK-positive status; and 1 (1.9%) had hepatosplenic T-cell lymphoma.

Determination of the MTD (part 1)

The primary end point of the study was to determine the MTD of Fol-CHOP in part 1 of the study, which was completed with 19 patients. In part 1, on days 1 and 8 of each cycle, patients were treated with 10, 15, 20, 25, and 30 mg/m^2 of Fol-CHOP per dose escalation, in 5 sequential cohorts. No patients experienced DLTs in cohorts 1, 2, 3, 4, and 5, and the maximum dose administered was pralatrexate 30 mg/m^2, which was declared the MTD and selected as the dose for part 2.

Efficacy: part 1 and part 2

Of 52 patients enrolled (part 1 + part 2), all were treated with at least 1 dose of pralatrexate. Of the 52 patients, 50 had at least 1 postbaseline tumor assessment and were included in the efficacy analysis. The best ORR observed in 50 evaluable patients was 86% (95% CI, 73.26-94.18), which included 33 patients (66.0%) with CR and 10 (20.0%) with PR. Two patients (4.0%) had a best overall response of stable disease, and 4 (8.0%) had progressive disease. The time to median of PFS was not estimable for this population because of the small sample size. Responses according to the dose level are shown in Table 3.

Median duration of response was not estimable for all cohorts at each dose level in part 1 because not enough patients had experienced an event (progression of disease or death) at the time of data analysis cutoff (1 patient each had an event at the 10 mg/m^2, 15 mg/m^2, and 25 mg/m^2 dose levels, and 8 patients had an event in the expansion cohort). Overall, 11 patients (22%) experienced progressive disease in this study. Time to median of PFS was not estimable for this population because of a small sample size.

In part 2, a total of 33 patients were treated with 30 mg/m^2 of pralatrexate in combination with CHOP; however, only 31 were evaluable. Of the 31, the end of treatment ORR (after 6 cycles) was observed in 26 patients (83.9%), with 20 patients (64.5%) reporting CR and 6 (19.4%) reporting PR. Four patients (12.9%) had a best overall response of progressive disease. The 95% CI of overall response (CR + PR) was found to be 66.27% to 94.55%.

Efficacy according to the PTCL subtype. The response per PTCL subtype is shown in Table 4. For PTCL NOS (n = 34), the most common histology, 71% achieved CR and 18% achieved PR as their best overall response.

Dosing modifications and patient discontinuation

There were pralatrexate dose modifications noted in this study and included 11 instances of dose delay because of an AE in 9 patients

Table 1. Summary of patient baseline characteristics

Parameter/statistic, n(%)	Part 1					Part 2	Total (N = 52)
	CHOP + pralatrexate 10 mg/m^2 (n = 4)	CHOP + pralatrexate 15 mg/m^2 (n = 3)	CHOP + pralatrexate 20 mg/m^2 (n = 3)	CHOP + pralatrexate 25 mg/m^2 (n = 3)	CHOP + pralatrexate 30 mg/m^2 (n = 6)	CHOP + pralatrexate 30 mg/m^2 (n = 33)	
Age, median (range), y	68.5 (55-74)	60.0 (18-73)	60.0 (53-72)	47.0 (31-58)	66.0 (43-76)	62.0 (19-78)	62.0 (18-78)
Age category, n (%), y							
<65	1 (25.0)	2 (66.7)	2 (66.7)	3 (100.0)	2 (33.3)	18 (54.5)	28 (53.8)
65-75	3 (75.0)	1 (33.3)	1 (33.3)	0	3 (50.0)	13 (39.4)	21 (40.4)
>75	0	0	0	0	1 (16.7)	2 (6.1)	3 (5.8)
Sex, n (%)							
Male	4 (100.0)	1 (33.3)	2 (66.7)	2 (66.7)	3 (50.0)	18 (54.5)	30 (57.7)
Female	0	2 (66.7)	1 (33.3)	1 (33.3)	3 (50.0)	15 (45.5)	22 (42.3)
Race, n (%)							
White or Caucasian	3 (75.0)	3 (100.0)	2 (66.7)	3 (100.0)	6 (100.0)	24 (72.7)	41 (78.8)
Black or African American	0	0	0	0	0	5 (15.2)	5 (9.6)
American Indian or Alaska Native	0	0	0	0	0	1 (3.0)	1 (1.9)
Asian	1 (25.0)	0	1 (33.3)	0	0	2 (6.1)	4 (7.7)
Other	0	0	0	0	0	1 (3.0)	1 (1.9)
Ethnicity, n (%)							
Hispanic or Latino	1 (25.0)	1 (33.3)	0	0	0	3 (9.1)	5 (9.6)
Not Hispanic or Latino	3 (75.0)	2 (66.7)	3 (100.0)	3 (100.0)	6 (100.0)	30 (90.9)	47 (90.4)
Subtype of PTCL, n (%)							
ALCL, ALK negative	1 (25.0)	2 (66.7)	0	0	0	4 (12.1)	7 (13.5)
ALCL, ALK positive	0	0	0	0	0	1 (3.0)	1 (1.9)
AITL	1 (25.0)	0	1 (33.3)	0	2 (33.3)	5 (15.2)	9 (17.3)
Hepatosplenic T-cell lymphoma	0	0	0	0	0	1 (3.0)	1 (1.9)
PTCL, NOS	2 (50.0)	1 (33.3)	2 (66.7)	3 (100)	4 (66.7)	22 (66.7)	34 (65.4)
Eastern Cooperative Oncology Group performance status, n (%)							
0 (fully active)	1 (25.0)	2 (66.7)	2 (66.7)	3 (100.0)	3 (50.0)	19 (57.6)	30 (57.7)
1 (restricted in physically strenuous activity but ambulatory)	2 (50.0)	0	1 (33.3)	0	2 (33.3)	11 (33.3)	16 (30.8)
2 (ambulatory and capable of all self-care but unable to carry out work)	0	1 (33.3)	0	0	1 (16.7)	3 (9.1)	5 (9.6)
Bone marrow finding, n (%)							
Lymphoma not present	1 (25.0)	1 (33.3)	1 (33.3)	2 (66.7)	3 (50.0)	17 (51.5)	25 (48.1)
Lymphoma present	2 (50.0)	0	1 (33.3)	1 (33.3)	3 (50.0)	9 (27.3)	16 (30.8)
Not evaluable	0	0	0	0	0	0	0

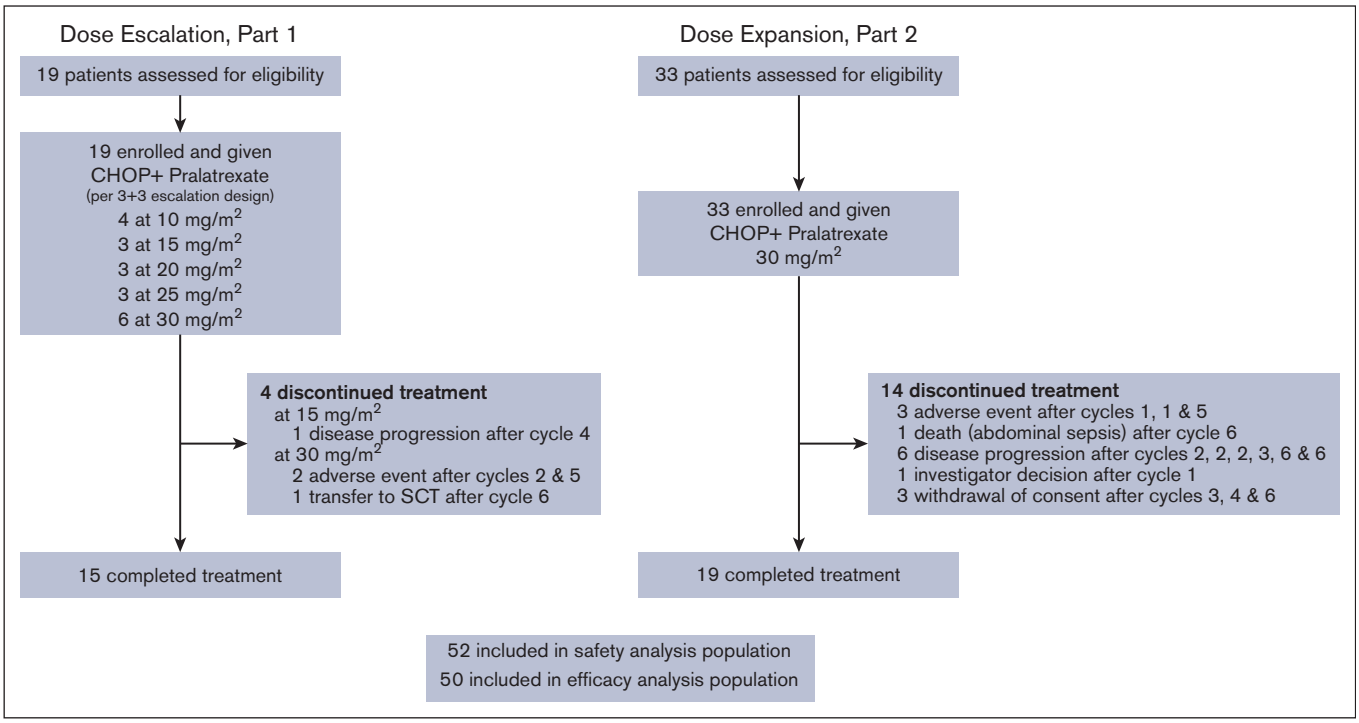

Figure 2. Patient disposition. SCT, stem cell transplant.

(cohort 2, n = 2; cohort 3, n = 2; cohort 5, n = 2; and expansion, n = 3) and 6 instances of dose reduction in 6 patients (cohort 5, n = 1; and expansion, n = 5). Details of the reasons for delay, timing of delays, and patient characteristics are included in supplemental Table 2. Two patients in cohort 5 are included in the dose-reduction and -delay groups. Of those patients who experienced a dose reduction, the best overall response was CR for 3 and PR for 2, and 1 patient (had 1 dose delayed and 1 reduced due to AEs) had progressive disease. Of those patients who had a dose delayed, the best overall response for 6 was CR and for 2 PR, and the same patient noted earlier, experiencing dose-reduction delay, had progressive disease.

A total of 18 patients discontinued from the study before completing all per protocol dosing and/or follow-up. Of the patients who discontinued, the best overall response was CR for 6 and PR for 4, and 2 had stable disease, 4 had progression of disease, and 2 were not evaluable.

Safety

TEAEs were reported for all 52 patients, with the most frequently reported being fatigue (75.0%), constipation (57.7%), mucosal inflammation and nausea (51.9% each), anemia (42.3%), vomiting (28.8%), diarrhea (26.9%), dizziness, neutropenia, and dyspnea (25.0% each). Thirty-five patients (67.3%) experienced grade 3/4 TEAEs, the most common of which were anemia (21.2%), neutropenia (19.2%), febrile neutropenia (11.5%), fatigue, mucosal inflammation, nausea, and vomiting (7.7% each).

Forty-nine patients (94.2%) experienced TEAEs considered to be related to pralatrexate treatment, the most common of which were fatigue (51.9%), mucosal inflammation (48.1%), nausea (44.2%), constipation (40.4%), anemia (36.5%), and vomiting (25.0%).

Fifty-one patients (98.1%) experienced TEAEs considered to be related to CHOP treatment, the most common of which were fatigue (53.8%), nausea (42.3%), constipation (50.0%), anemia (36.5%), vomiting (25.0%), mucosal inflammation, and neutropenia (23.1% each).

A summary of TEAEs by severity experienced by >1 patients is included in Table 5. A table of all reported TEAEs according to the severity are detailed in supplemental Table 3.

Because of TEAEs, 9 patients were discontinued from pralatrexate treatment and 7 from CHOP. The AEs that resulted in discontinuation are detailed in Table 6. Eight patients (1 in cohort 5 and 7 in expansion) required a pralatrexate dose and/or schedule reduction due to AEs, whereas 4 patients, all in expansion, required a CHOP dose and/or schedule reduction.

Nineteen patients (36.5%) experienced a total of 35 SAEs. SAEs reported for >1 patient included febrile neutropenia 6 (11.5%), anemia 3 (5.8%), nausea, and pneumonia aspiration (3.8% each). SAEs were considered to be related to pralatrexate for 10 patients (19.2%), including 3 patients (5.8%) each with SAEs of anemia and febrile neutropenia; all other pralatrexate-related SAEs were reported for 1 patient (1.9%) each. SAEs were considered to be related to CHOP for 12 patients (23.1%), including 4 (7.7%) with febrile neutropenia, 3 (5.8%) with anemia, and 2 (3.8%) with nausea; all other CHOP-related SAEs were reported for 1 patient (1.9%) each.

Overall, 1 patient (1.9%) died during the study or within 30 days of the last dose of the study treatment. The cause of death for the patient was abdominal sepsis.

Table 2. Summary of pralatrexate exposure

		Cohort 1 CHOP + pralatrexate 10 mg/m^2 (n = 4)	Cohort 2 CHOP + pralatrexate 15 mg/m^2 (n = 3)	Cohort 3 CHOP + pralatrexate 20 mg/m^2 (n = 3)	Cohort 4 CHOP + pralatrexate 25 mg/m^2 (n = 3)	Cohort 5 CHOP + pralatrexate 30 mg/m^2 (n = 6)	Expansion CHOP + pralatrexate 30 mg/m^2 (n = 33)	Total (N = 52)
Number of cycles administered	n	4	3	3	3	6	33	52
	Mean	6.00	5.33	6.00	6.00	5.17	4.88	5.15
	SD	0.000	1.155	0.000	0.000	1.602	1.816	1.601
	Median	6.00	6.00	6.00	6.00	6.00	6.00	6.00
	Min, Max	6.0, 6.0	4.0, 6.0	6.0, 6.0	6.0, 6.0	2.0, 6.0	1.0, 6.0	1.0, 6.0
Total cumulative dose received (mg/m^2)	n	4	3	3	3	6	33	52
	Mean	247.95	279.20	474.67	598.00	541.33	490.84	471.02
	SD	38.630	22.098	16.653	93.016	246.676	223.193	213.381
	Median	262.50	281.60	480.00	600.00	566.50	532.00	484.10
	Min, Max	190.8, 276.0	256.0, 300.0	456.0, 488.0	504.0, 690.0	189.0, 804.0	50.0, 864.0	50.0, 864.0
Relative dose intensity (%)	n	4	3	3	3	6	33	52
	Mean	102.07	100.18	99.36	98.14	97.04	97.64	98.19
	SD	2.585	2.210	2.372	1.566	14.163	11.831	10.500
	Median	101.76	99.80	99.48	97.49	101.78	100.40	100.39
	Min, Max	99.6, 105.2	98.2, 102.6	96.9, 101.7	97.0, 99.9	68.5, 106.9	69.2, 137.5	68.5, 137.5

PKs

The PK parameters obtained after the cycle-1 day-1 dose of pralatrexate (PDX-10a and PDX-10b) in the plasma are presented in supplemental Table 5. The rate of absorption for PDX-10b was found to be 13.4% higher than that of PDX-10a. The extent of absorption (area under the curve) for PDX-10b was found to be 44.8% higher than that of PDX-10a. $T_{1/2}$ and T_{max} were found to be similar for both analytes, at ~4.5 hours and 0.1 hour, respectively. The total clearance for PDX-10a was found to be 47% higher than that of PDX-10b. The volume of distribution for PDX-10a was found to be 52% higher than that of PDX-10b.

Discussion

This was the first prospective study, to our knowledge, to evaluate the Fol-CHOP for patients with PTCL. A total of 52 patients were enrolled in the study, and 33 patients in the part 2, expansion, phase received pralatrexate at dose of 30 mg/m^2 in combination with CHOP every 21 days for up to 6 cycles. The primary objective of the part 1 of this study was to evaluate the MTD of pralatrexate in combination with CHOP and, for the part 2, characterize safety and efficacy of the MTD in an expansion cohort. The Fol-CHOP regimen was reasonably well tolerated and resulted in an 86% ORR and 66% CR rate. Median duration of response was not estimable because not enough patients had experienced an event (progression of disease or death) at the time of data analysis cutoff, and time to median of PFS was not estimable for this population because of the small sample size. We recognize this as a limitation of these study results; because this is a phase 1 protocol and did not stipulate long-term follow-up data collection on eCRF; however, PFS and EFS will be captured in the design of an upcoming phase 3 study.

The toxicity profile of the combination therapy was manageable; the most common grade ≥3 AEs were anemia (21.2%), neutropenia (19.2%), febrile neutropenia (11.5%), fatigue, mucosal inflammation, nausea, and vomiting (7.7% each).

CHOP has often been used as a comparator in PTCL treatment trials, with an OS at 24 months of 50% to 76%.[23-26] In efforts to improve outcomes, a number of other agents combined with CHOP have been evaluated in the past decade, including belinostat, romidepsin, and azacitidine. In the Bel-CHOP study, patients with PTCL, with a median age of 63 years, received belinostat (1000 mg/m^2 once daily) + standard CHOP for 6 cycles, resulting in an ORR of 86% and CR of 71%.[26] All patients experienced AEs, and serious events occurred in 43%, including febrile neutropenia (17%) and pyrexia (13%).[27] A recent phase 3 trial combining romidepsin with CHOP reported a median PFS of 12.0 months compared with 10.2 months for CHOP alone, with an ORR of 63% vs 60%, respectively.[23] Although the addition of romidepsin to CHOP did not lead to improvements in response rates or OS and increased the frequency of grade ≥ 3 TEAEs, including thrombocytopenia (50%), neutropenia (49%), anemia (47%), and leukopenia (32%), an exploratory analysis of centrally confirmed TFH lymphomas, such as AITL, did identify extended PFS in the romidepsin with CHOP arm (19.5 months) compared with CHOP alone (10.6 months).[23] Oral azacitidine has been previously studied in AITL but more recently studied in PTCL in addition to standard CHOP. A phase 2 study of 17 patients with AITL or PTCL-TFH

Table 3. Tumor responses according to the dose level evaluable population of 50 patients

	Part 1					Part 2	
	Cohort 1 10 mg/m^2 (n = 4), n (%)	Cohort 2 15 mg/ m^2 (n = 3), n (%)	Cohort 3 20 mg/ m^2 (n = 3), n (%)	Cohort 4 25 mg/ m^2 (n = 3), n (%)	Cohort 5 30 mg/ m^2 (n = 6), n (%)	Expansion 30 mg/ m^2 (n = 31), n (%)	Total (N = 50), n (%)
Overall response per lugano classification							
CR	3 (75.0)	1 (33.3)	2 (66.7)	2 (66.7)	5 (83.3)	20 (64.5)	33 (66.0)
PR	1 (25.0)	1 (33.3)	1 (33.3)	1 (33.3)	0	6 (19.4)	10 (20.0)
Stable disease	0	1 (33.3)	0	0	1 (16.7)	0	2 (4.0)
Progressive disease	0	0	0	0	0	4 (12.9)	4 (8.0)
Not evaluable	0	0	0	0	0	1 (3.2)	1 (2.0)
Objective response rate							
CR	3 (75.0)	1 (33.3)	2 (66.7)	2 (66.7)	5 (83.3)	20 (64.5)	33 (66.0)
95% CI (%)	19.41, 99.37	0.84, 90.57	9.43, 99.16	9.43, 99.16	35.88, 99.58	45.37, 80.77	51.23, 78.79
Overall response (CR + PR)	4 (100.0)	2 (66.7)	3 (100.0)	3 (100.0)	5 (83.3)	26 (83.9)	43 (86.0)
95% CI (%)	39.76, 100.0	9.43, 99.16	29.24, 100.0	29.24, 100.0	35.88, 99.58	66.27, 94.55	73.26, 94.18

reported CR rates of 88% for patients with AITL or PTCL-TFH, with neutropenia (71%) being the most common.[28]

A recent review of 55 clinical studies that used CHOP or CHOP-like regimens as comparators for novel combinations concluded that with only 1 exception (BV + cyclophosphamide, doxorubicin, and prednisone [A + CHP], as reported in the ECHELON-2 trial), other combinations showed no statistically significant benefit over CHOP alone, in terms of OS or PFS in patients with PTCL.[15,26,29]

Comparison of outcomes in PTCL studies should be made with the recognition that there are wide variations in the characteristics of enrolled participants. Median ages that have been reported range from 33 to 74 years, whereas in this study, the median age was 62 years, gender proportions were variable, and there was a mix of PTCL subtypes. In our study, the addition of Fol-CHOP resulted in favorable OR and CR rates. Although pralatrexate led to an ORR of 29% patients with PTCL in the landmark PROPEL study, a lower response rate in patients with AITL subtype was seen. However, other studies, including retrospective analyses, found a more favorable response in AITL. An international case match control analysis of PROPEL was conducted, reporting superior OS for patients treated on PROPEL compared with historical controls from an international PTCL database that were rigorously matched against PROPEL criteria using propensity score matching algorithm. Notably, the OS estimates for AITL subtype were 5.5 months for the historical controls and 9.77 months with PROPEL.[30]

Chihara et al reported a median OS after first, second, and third relapse for patients with AITL of 15.0, 8.3, and 6.0 months, respectively.[31] Pralatrexate was also evaluated as an investigator-selected single-agent comparator in the Lumiere Study of alisertib in R/R PTCL, which reported an ORR of 43% for pralatrexate and 33% for alisertib.[18]

Within the PTCL trials including pralatrexate, the development of oral mucositis grade ≥2 has been reported at a rate of 52%.[13] The use of leucovorin (d,l-folinic acid) as an adjunct to pralatrexate therapy has been studied as a strategy to mitigate mucositis in patients with PTCL and has demonstrated a significant reduction in the rates of grade ≥2 and grade ≥3 mucositis.[20] To our knowledge, this study was one of the first studies to investigate the prospective use of calcium leucovorin for mucositis prophylaxis. In our study, patients were instructed to take leucovorin tablets (25 mg) 3 times a day for 2 days, beginning 24 hours after each pralatrexate treatment, as prophylaxis. We reported an overall incidence of any mucositis of 51.9%: 28.8% with grade 1 severity, 15.4% with grade 2 severity, 7.7% with grade 3 severity, and no cases of grade 4 mucositis. Comparatively, in the PROPEL trial, 71% experienced any grade of mucositis, with 18% having grade 3 and 4% having grade 4 severity.[13]

The primary objective of this study was met; the Fol-CHOP regimen was reasonably well tolerated with an MTD of 30 mg/m^2 and demonstrated a promising ORR of 83.9% (20 CRs and 6 PRs)

Table 4. Tumor response according to the subtype

Subtype of PTCL	ALCL, ALK negative (n = 7)	ALCL, ALK positive (n = 1)	AITL (n = 9)	Hepatosplenic T-cell lymphoma (n = 1)	PTCL, NOS (n = 34)
CR	3 (43%)	1 (100%)	5 (56%)	0	24 (71%)
PR	3 (43%)	0	2 (22%)	0	6 (18%)
Stable disease	1 (14%)	0	1 (11%)	0	0
Progressive disease	0	0	0	0	4 (12%)
Not evaluable	0	0	1 (11%)	1 (100%)	0

Table 5. TEAEs according to the severity-safety population (experienced by more than 1 patient)

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blood and lymphatic system disorders	3 (5.8%)	9 (17.3%)	19 (36.5%)	6 (11.5%)	0	37 (71.2%)
Anemia	2 (3.8%)	9 (17.3%)	11 (21.2%)	0	0	22 (42.3%)
Febrile Neutropenia	0	1 (1.9%)	6 (11.5%)	0	0	7 (13.5%)
Leukopenia	1 (1.9%)	0	0	1 (1.9%)	0	2 (3.8%)
Lymphopenia	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)
Neutropenia	1 (1.9%)	2 (3.8%)	5 (9.6%)	5 (9.6%)	0	13 (25.0%)
Thrombocytopenia	0	2 (3.8%)	0	1 (1.9%)	0	3 (5.8%)
Cardiac disorders, tachycardia	2 (3.8%)	1 (1.9%)	0	0	0	3 (5.8%)
Ear and labyrinth disorders, ear pain	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)
Eye disorders	11 (21.2%)	2 (3.8%)	0	0	0	13 (25.0%)
Dry eye	6 (11.5%)	0	0	0	0	6 (11.5%)
Lacrimation increased	5 (9.6%)	1 (1.9%)	0	0	0	6 (11.5%)
Vision blurred	8 (15.4%)	1 (1.9%)	0	0	0	9 (17.3%)
Gastrointestinal disorders	20 (38.5%)	18 (34.6%)	8 (15.4%)	0	0	46 (88.5%)
Abdominal pain	2 (3.8%)	2 (3.8%)	1 (1.9%)	0	0	5 (9.6%)
Constipation	18 (34.6%)	10 (19.2%)	2 (3.8%)	0	0	30 (57.7%)
Diarrhea	9 (17.3%)	5 (9.6%)	0	0	0	14 (26.9%)
Dyspepsia	2 (3.8%)	1 (1.9%)	1 (1.9%)	0	0	4 (7.7%)
Gastritis	0	2 (3.8%)	0	0	0	2 (3.8%)
Gastroesophageal reflux disease	4 (7.7%)	4 (7.7%)	1 (1.9%)	0	0	9 (17.3%)
Nausea	12 (23.1%)	10 (19.2%)	4 (7.7%)	0	0	26 (50.0%)
Oral pain	5 (9.6%)	6 (11.5%)	1 (1.9%)	0	0	12 (23.1%)
Stomatitis	5 (9.6%)	4 (7.7%)	2 (3.8%)	0	0	11 (21.2%)
Vomiting	6 (11.5%)	5 (9.6%)	4 (7.7%)	0	0	15 (28.8%)
General disorders and administration site conditions	16 (30.8%)	23 (44.2%)	8 (15.4%)	1 (1.9%)	0	48 (92.3%)
Chest pain	3 (5.8%)	0	0	0	0	3 (5.8%)
Fatigue	16 (30.8%)	19 (36.5%)	3 (5.8%)	1 (1.9%)	0	39 (75.0%)
Local swelling	2 (3.8%)	1 (1.9%)	1 (1.9%)	0	0	4 (7.7%)
Mucosal inflammation	15 (28.8%)	8 (15.4%)	4 (7.7%)	0	0	27 (51.9%)
Edema peripheral	2 (3.8%)	1 (1.9%)	0	0	0	3 (5.8%)
Pyrexia	5 (9.6%)	4 (7.7%)	0	0	0	9 (17.3%)
Infections and infestations	7 (13.5%)	9 (17.3%)	4 (7.7%)	1 (1.9%)	1 (1.9%)	22 (42.3%)
Candida infection	0	3 (5.8%)	0	0	0	3 (5.8%)
Nasopharyngitis	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)
Pneumonia	0	1 (1.9%)	1 (1.9%)	0	0	2 (3.8%)
Upper respiratory tract infection	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)
Investigations	9 (17.3%)	5 (9.6%)	7 (13.5%)	5 (9.6%)	0	26 (50.0%)
Alanine aminotransferase level increased	6 (11.5%)	0	2 (3.8%)	0	0	8 (15.4%)
Aspartate aminotransferase level increased	5 (9.6%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0	8 (15.4%)
Blood creatinine level increased	2 (3.8%)	1 (1.9%)	1 (1.9%)	0	0	4 (7.7%)
Hematocrit level decreased	0	2 (3.8%)	0	0	0	2 (3.8%)
Lymphocyte count decreased	1 (1.9%)	1 (1.9%)	2 (3.8%)	1 (1.9%)	0	5 (9.6%)
Neutrophil count decreased	0	0	2 (3.8%)	3 (5.8%)	0	5 (9.6%)
Platelet count decreased	3 (5.8%)	3 (5.8%)	0	1 (1.9%)	0	7 (13.5%)
Weight decreased	5 (9.6%)	0	0	0	0	5 (9.6%)
White blood cell count decreased	0	3 (5.8%)	1 (1.9%)	0	0	4 (7.7%)
Metabolism and nutrition disorders	15 (28.8%)	5 (9.6%)	3 (5.8%)	0	0	23 (44.2%)

Table 5 (continued)

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Decreased appetite	10 (19.2%)	2 (3.8%)	0	0	0	12 (23.1%)
Dehydration	1 (1.9%)	3 (5.8%)	1 (1.9%)	0	0	5 (9.6%)
Hyperglycemia	2 (3.8%)	0	0	0	0	2 (3.8%)
Hyperuricemia	4 (7.7%)	0	0	0	0	4 (7.7%)
Hypokalemia	5 (9.6%)	1 (1.9%)	0	0	0	6 (11.5%)
Hypomagnesemia	4 (7.7%)	0	0	0	0	4 (7.7%)
Musculoskeletal and connective tissue disorders	10 (19.2%)	8 (15.4%)	1 (1.9%)	1 (1.9%)	0	20 (38.5%)
Arthralgia	2 (3.8%)	0	0	0	0	2 (3.8%)
Back pain	1 (1.9%)	2 (3.8%)	1 (1.9%)	0	0	4 (7.7%)
Bone pain	2 (3.8%)	3 (5.8%)	0	0	0	5 (9.6%)
Muscle spasms	2 (3.8%)	0	0	0	0	2 (3.8%)
Myalgia	5 (9.6%)	3 (5.8%)	0	0	0	8 (15.4%)
Nervous system disorders	22 (42.3%)	6 (11.5%)	1 (1.9%)	0	0	29 (55.8%)
Dizziness	10 (19.2%)	3 (5.8%)	0	0	0	13 (25.0%)
Headache	5 (9.6%)	0	1 (1.9%)	0	0	6 (11.5%)
Hypoesthesia	3 (5.8%)	0	0	0	0	3 (5.8%)
Memory impairment	5 (9.6%)	2 (3.8%)	0	0	0	7 (13.5%)
Neuropathy peripheral	9 (17.3%)	2 (3.8%)	0	0	0	11 (21.2%)
Peripheral sensory neuropathy	6 (11.5%)	1 (1.9%)	0	0	0	7 (13.5%)
Psychiatric disorders	11 (21.2%)	4 (7.7%)	0	0	0	15 (28.8%)
Anxiety	1 (1.9%)	2 (3.8%)	0	0	0	3 (5.8%)
Depression	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)
Insomnia	8 (15.4%)	2 (3.8%)	0	0	0	10 (19.2%)
Renal and urinary disorders	7 (13.5%)	1 (1.9%)	0	0	0	8 (15.4%)
Dysuria	4 (7.7%)	0	0	0	0	4 (7.7%)
Pollakiuria	3 (5.8%)	0	0	0	0	3 (5.8%)
Respiratory, thoracic, and mediastinal disorders	23 (44.2%)	4 (7.7%)	3 (5.8%)	0	0	30 (57.7%)
Cough	4 (7.7%)	2 (3.8%)	0	0	0	6 (11.5%)
Dyspnea	12 (23.1%)	1 (1.9%)	0	0	0	13 (25.0%)
Epistaxis	2 (3.8%)	0	0	0	0	2 (3.8%)
Oropharyngeal pain	5 (9.6%)	0	0	0	0	5 (9.6%)
Pneumonia aspiration	0	0	2 (3.8%)	0	0	2 (3.8%)
Rhinorrhea	3 (5.8%)	0	0	0	0	3 (5.8%)
Sinus congestion	2 (3.8%)	0	0	0	0	2 (3.8%)
Skin and subcutaneous tissue disorders	11 (21.2%)	7 (13.5%)	0	0	0	18 (34.6%)
Alopecia	2 (3.8%)	4 (7.7%)	0	0	0	6 (11.5%)
Rash	7 (13.5%)	2 (3.8%)	0	0	0	9 (17.3%)
Skin Exfoliation	2 (3.8%)	0	0	0	0	2 (3.8%)
Vascular disorders	2 (3.8%)	5 (9.6%)	1 (1.9%)	1 (1.9%)	0	9 (17.3%)
Deep vein thrombosis	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)
Embolism	0	2 (3.8%)	0	0	0	2 (3.8%)
Hypertension	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)
Hypotension	1 (1.9%)	1 (1.9%)	0	0	0	2 (3.8%)

at CHOP + pralatrexate 30 mg/m^2, as assessed by treating investigators. The nature of this being a phase 1 trial, without long-term survival data to assess durability of responses, precludes any conclusions as to the superiority of particular regimens. The ORR was encouraging, comparable with the ORR seen in other studies of CHOP-based regimens in PTCL, and the toxicity profile was

Table 6. TEAEs leading to dose discontinuation

Dose disruption				
Patient number (n = 9)	Treatment group Cohort no. or expansion (dose)	AE term	Action taken with pralatrexate	Action taken with CHOP
1	Expansion (30 mg/m^2)	Anemia	Drug withdrawn	Drug withdrawn
2	Cohort 5 (30 mg/m^2)	Hypovolemic shock	Drug withdrawn	Drug withdrawn
3	Expansion (30 mg/m^2)	Neutrophil count decreased Aspartate aminotransferase increased Febrile neutropenia	Drug withdrawn Drug withdrawn Drug withdrawn	Drug withdrawn Drug withdrawn Drug withdrawn
4	Expansion (30 mg/m^2)	Mucosal inflammation	Drug withdrawn	Dose not changed
5	Expansion (30 mg/m^2)	Abdominal sepsis	Drug withdrawn	Drug withdrawn
6	Cohort 5 (30 mg/m^2)	Neutrophil count decreased	Drug withdrawn	Dose not changed
7	Expansion (30 mg/m^2)	Neutropenia	Drug withdrawn	Drug withdrawn
8	Expansion (30 mg/m^2)	Nausea	Drug withdrawn	Drug withdrawn
9	Expansion (30 mg/m^2)	Confusional state Fatigue	Drug withdrawn	Drug withdrawn

manageable, although dose adjustments for each component of Fol-CHOP were not infrequent. Other dosing strategies for Fol-CHOP may need to be explored to allow for a higher dose intensity. These findings have provided supportive evidence toward the development of an upcoming clinical trial (2024), further investigating the Fol-CHOP treatment regimen as a firstline treatment for PTCL.

Acknowledgments

The authors thank the patients who participated in this trial, their families, the investigators, and staff at all the clinical sites. The authors acknowledge April Ingram for her valuable administrative support and writing contributions.

This work was supported by Acrotech Biopharma Inc.

Authorship

Contribution: All authors contributed to the concept and study design; analyzed and interpreted data, reviewed the first draft of manuscript, provided critical scientific input, gave final approval for manuscript, and were accountable for all aspects of the work.

Conflict-of-interest disclosure: S.P.I. reports consultancy fee from CRISPR, Merck, Rhizen, Seagen, Acrotech, Innate, Myeloid Therapeutics, AstraZeneca, Dren-Bio, Ono, and Trillium/Pfizer; research funding from CRISPR, Rhizen, Seagen, Acrotech, Innate, Myeloid Therapeutics, AstraZeneca, Dren-Bio, Ono, Citius, and Trillium/Pfizer; honoraria from the American Society of Hematology, American Society for Transplantation and Cellular Therapy, Seagen, Curabio, and Target Oncology; and membership on a board or advisory committee of Seagen, Acrotech, and Trillium/Pfizer. S.K.B. reports consultancy fee from Acrotech, Affimed, and Kyowa Kirin; membership on a board or advisory committee of Acrotech, Affimed, Daiichi-Sankyo, Janssen, Kyowa Kirin, and Seagen. P.B.J. declares no competing financial interests.

ORCID profile: S.P.I., 0000-0002-1646-813X.

Correspondence: Swaminathan P. Iyer, Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd, Unit 429, Houston, TX, 77030; email: spiyer@mdanderson.org.

References

1. Rüdiger T, Weisenburger DD, Anderson JR, et al. Non-Hodgkin's Lymphoma Classification Project. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol*. 2002;13(1):140-149.
2. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26(25):4124-4130.
3. Savage KJ. Therapies for peripheral T-cell lymphomas. *Hematology Am Soc Hematol Educ Program*. 2011;2011:515-524.
4. Campo E, Gaulard P, Zucca E, et al. Report of the European Task Force on lymphomas: workshop on peripheral T-cell lymphomas. *Ann Oncol*. 1998;9(8):835-843.
5. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. *Br J Haematol*. 2006;134(2):202-207.
6. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. *Blood*. 2011;117(25):6756-6767.
7. Tang T, Tay K, Quek R, et al. Peripheral T-cell lymphoma: review and updates of current management strategies. *Adv Hematol*. 2010;2010:624040.
8. Abouyabis AN, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. *ISRN Hematol*. 2011;2011:623924.

9. Horwitz SM, Ansell S, Ai WZ, et al. T-cell lymphomas, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022; 20(3):285-308.
10. Ganjoo K, Hong F, Horning SJ, et al. Bevacizumab and cyclosphosphamide, doxorubicin, vincristine and prednisone in combination for patients with peripheral T-cell or natural killer cell neoplasms: an Eastern Cooperative Oncology Group study (E2404). *Leuk Lymphoma*. 2014;55(4):768-772.
11. Kim JG, Sohn SK, Kim DH, Baek JH, Park TI, Lee KB. Phase II study of cyclophosphamide,epirubicin, vincristine, prednisone, and etoposide (CEOP-E) for aggressive non-Hodgkin 's lymphoma. *J Korean Med Sci*. 2004;19(6):820-825.
12. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Société Francaise de Greffe de Moëlle et de Thérapie Cellulaire. *J Clin Oncol*. 2008;26(14):2264-2271.
13. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal Propel study. *J Clin Oncol*. 2011;29(9):1182-1189.
14. Schmitz N, Truemper L, Bouabdallah K, et al. A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL. *Blood*. 2021;137(19):2646-2656.
15. Horwitz S, O'Connor OA, Pro B, et al; ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229-240.
16. Folotyn. Prescribing information, Spectrum Pharmaceuticals. 2018. Accessed 11 January 2023.
17. O'Connor OA, Marchi E, Kim WS. Case match control analysis of propel reveals a survival advantage for patients with relapsed PTCL receiving pralatrexate: a novel approach to benchmark drugs in rare diseases. *Hematol Oncol*. 2017;35:250.
18. O'Connor OA, Özcan M, Jacobsen ED, et al. Lumiere study investigators. randomized phase III study of alisertib or investigator's choice (selected single agent) in patients with relapsed or refractory peripheral T-cell lymphoma. *J Clin Oncol*. 2019;37(8):613-623.
19. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016; 127(20):2375-2390.
20. Shustov AR, Shinohara MM, Dakhil SR, Bhat G, Zain JM. Management of mucositis with the use of leucovorin as adjunct to pralatrexate in treatment of peripheral t-cell lymphomas (PTCL) – results from a prospective multicenter phase 2 clinical trial. *Blood*. 2018;132(suppl 1):2910.
21. Appling DR. Compartmentation of folate-mediated one-carbon metabolism in eukaryotes. *FASEB J*. 1991;5(12):2645-2651.
22. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.
23. Bachy E, Camus V, Thieblemont C, et al. Final analysis of the Ro-CHOP phase III study (conducted by LYSA): romidepsin plus CHOP in patients with peripheral T-cell lymphoma. *J Clin Oncol*. 2022;40(3):242-251.
24. Gleeson M, Peckitt C, To YM, et al. CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): a phase 2, multicentre, randomised, open-label trial. *Lancet Haematol*. 2018;5(5):e190-e200.
25. Li L, Duan W, Zhang L, et al. The efficacy and safety of gemcitabine, cisplatin, prednisone, thalidomide versus CHOP in patients with newly diagnosed peripheral T-cell lymphoma with analysis of biomarkers. *Br J Haematol*. 2017;178(5):772-780.
26. Ashaye AO, Burnett H, Abogunrin S, Panchmatia H, Ovcinnikova O, Dalal M. The clinical and economic burden of peripheral T-cell lymphoma: a systematic literature review. *Future Oncol*. 2022;18(4):519-535.
27. Johnston PB, Cashen AF, Nikolinakos PG, et al. Belinostat in combination with standard cyclophosphamide, doxorubicin, vincristine and prednisone as first-line treatment for patients with newly diagnosed peripheral T-cell lymphoma. *Exp Hematol Oncol*. 2021;10(1):15.
28. Ruan J, Moskowitz AJ, Mehta-Shah N, et al. Multicenter phase 2 study of oral azacitidine (CC-486) plus CHOP as initial treatment for peripheral T-cell lymphoma. *Blood*. 2023;141(18):2194-2205.
29. Horwitz SM, O'Connor OA, Pro B, Illidge T, et al. The ECHELON-2 trial: 5-year results of a randomized, double-blind, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in frontline treatment of patients with CD30-positive peripheral T-cell lymphoma. *Blood*. 2020;136(suppl 1): 3-5.
30. O'Connor OA, Marchi E, Volinn W, Shi J, Mehrling T, Kim WS. Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study. *JNCI Cancer Spectr*. 2018;2(4):pky038.
31. Chihara D, Fanale MA, Miranda RN, et al. The survival outcome of patients with relapsed/refractory peripheral T-cell lymphoma-not otherwise specified and angioimmunoblastic T-cell lymphoma. *Br J Haematol*. 2017;176(5):750-758.