bjh research paper

A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial

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Received 15 July 2015; accepted for publication 6 October 2015

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Summary

Peripheral T-cell lymphomas (PTCL) have suboptimal outcomes using conventional CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. The anti-folate pralatrexate, the first drug approved for patients with relapsed/refractory PTCL, provided a rationale to incorporate it into the front-line setting. This phase 2 study evaluated a novel front-line combination whereby cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternated with pralatrexate (CEOP-P) in PTCL. Patients achieving a complete or partial remission (CR/PR) were eligible for consolidative stem cell transplantation (SCT) after 4 cycles. Thirty-three stage II-IV PTCL patients were treated: 21 PTCL-not otherwise specified (64%), 8 angioimmunoblastic T cell lymphoma (24%) and 4 anaplastic large cell lymphoma (12%). The majority (61%) had stage IV disease and 46% were International Prognostic Index high/intermediate or high risk. Grade 3–4 toxicities included anaemia (27%), thrombocytopenia (12%), febrile neutropenia (18%), mucositis (18%), sepsis (15%), increased creatinine (12%) and liver transaminases (12%). Seventeen patients (52%) achieved a CR. The 2-year progression-free survival and overall survial, were 39% (95% confidence interval 21–57) and 60% (95% confidence interval 39–76), respectively. Fifteen patients (45%) (12 CR) received SCT and all remained in CR at a median follow-up of 21·5 months. CEOP-P did not improve outcomes compared to historical data using CHOP. Defining optimal front line therapy in PTCL continues to be a challenge and an unmet need.

Keywords: T-cell lymphoma, therapy, clinical trials.

First published online 2 December 2015
doi: 10.1111/bjh.13855

Peripheral Natural Killer (NK)/T cell lymphomas (PTCL) represent approximately 10% of all non-Hodgkin lymphomas (NHL) and, compared to B-cell NHL, are associated with a poorer prognosis (Savage, 2005). In the World Health Organization (WHO) classification, mature T and NK neoplasms are subdivided into 21 histological sub-types (Swerdlow *et al*, 2008). The various sub-entities are molecularly and clinically heterogeneous and the three most common subtypes of nodal PTCL in the Western hemisphere include PTCL-not otherwise specified (NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T cell lymphoma (AITL).

Currently, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) is considered a standard therapy for PTCL (Pinter-Brown *et al*, 2014). With the exception of anaplastic lymphoma kinase (ALK)-positive ALCL, most PTCL patients will either not achieve a complete remission (CR) or relapse after initial treatment with anthracycline-based regimens (Vose *et al*, 2008). In a meta-analysis of 31 studies of patients with PTCL treated with CHOP (n = 2912), excluding ALCL cases, the estimated 5-year overall survival (OS) was only 37·3% [95% confidence interval (CI) 35·1–39·6] (Abouyabis *et al*, 2011). More intensive chemotherapy regimens have, at best, shown only modest improvement when compared to historical controls with CHOP and have not been definitively proven to be superior in randomized trials (Simon *et al*, 2010; Abouyabis *et al*, 2011).

The German High Grade Lymphoma Study Group analysed a subset of patients with PTCL treated on 7 different protocols in which etoposide was added to CHOP (CHOEP) administered every 14 days. The authors found that younger patients (<60 years) with a normal lactic acid dehydrogenase who were treated with CHOEP had a significant improvement in event-free survival (EFS) compared to those treated with CHOP, although no difference in OS was observed. The greatest benefit was seen in the ALK-positive subset, with a trend towards improved EFS observed in the other nodal PTCLs (Schmitz *et al*, 2010).

Intensifying upfront therapy with high dose therapy and stem cell transplantation (HDT/SCT) has also been explored, suggesting some improvement in outcomes compared to historical results seen with CHOP. However, refractory disease to induction chemotherapy continues to be a challenge, limiting the proportion of patients able to undergo HDT/SCT (Reimer *et al*, 2009; d'Amore *et al*, 2012).

Pralatrexate, a novel anti-folate, was the first agent to receive US Food and Drug Administration (FDA) approval for the treatment of relapsed or refractory PTCL, with a 29% overall response rate (ORR) (O'Connor *et al*, 2011). In a multicentre phase 2 study of pralatrexate administered weekly for 6 weeks of a 7-week cycle, 63% of responders demonstrated reduction in disease burden by the end of cycle 1. The median duration of response and OS were 10·1 months (range, 1–673 days) and 14·5 months, respectively. Given the rarity and heterogeneity of PTCL, this was at the time the largest data set showing activity of a single agent in this disease.

With the goal to optimize the development of a new front line strategy, various approaches that individually had some success were combined. These included moving away from multi-drug resistance (MDR)-related anthracycline-based regimens, such as standard CHOP, and incorporating novel agents (pralatrexate) in up-front regimens. With these factors in mind, we tested a non-anthracycline containing regimen (cyclophosphamide, etoposide, vincristine and prednisone [CEOP]) alternating with pralatrexate (P). Consolidation with HDT/SCT for patients in remission as part of front line therapy for appropriate patients was at the discretion of the treating physician.

We hypothesized that this novel upfront regimen would result in a higher CR rate than historically observed from CHOP-like treatments and would thus allow more PTCL patients (if eligible) to receive HDT/SCT as consolidation.

Patients and methods

This open-label phase II study was conducted at academic sites participating in an informal working group, the 'T Cell Consortium', and approved by the institutional review board at each institution. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient. The University of Nebraska Medical Center provided data oversight. Patients ≥18 years with PTCL stages II–IV with no prior therapy, Karnofsky Performance Status > 70 and adequate end organ function were eligible. Eligible histologies included PTCL-NOS, AILT, ALCL (ALK positive patients were only allowed if the International Prognostic Index [IPI] was ≥3). Prior to each cycle the absolute neutrophil count was required to be $>1{\cdot}0 \times 10^9$/l, and platelet count $>0{\cdot}1 \times 10^9$/l. Detailed dose modification guidelines for hematological toxicities were built into the protocol (Table SI). Each cycle consisted of CEOP (A) administered as: cyclophosphamide 750 mg/m^2 IV day 1, etoposide 100 mg/m^2 IV days 1–3 (or 100 mg/m^2 IV day 1 and 200 mg/m^2 PO days 2–3), vincristine 2 mg IV day 1 and prednisone 100 mg/day ×5 alternating with P (B) 30 mg/m^2 IV days 15, 22 and 29. Growth factors were used to support both cycles of therapy (Fig 1). All patients received vitamin B12 (1 mg) intramuscular injection every 8–10 weeks and during B cycles oral folic acid (1·0–1·25 mg) daily. Patients with methylmalonic acid (MMA) levels ≥ 200 nmol/l or homocysteine (Hcy) ≥10 μmol/l at screening received supplementation > 10 days prior to the first pralatrexate dose (O'Connor *et al*, 2011).

Response assessment was performed by computerized tomography (CT) or positron emission tomography (PET)/CT based on the investigator's preference after cycles 2, 4 and 6. Response was assessed by the treating physician according to the Cheson Revised response criteria (Cheson *et al*, 2007) or International Harmonization Project criteria

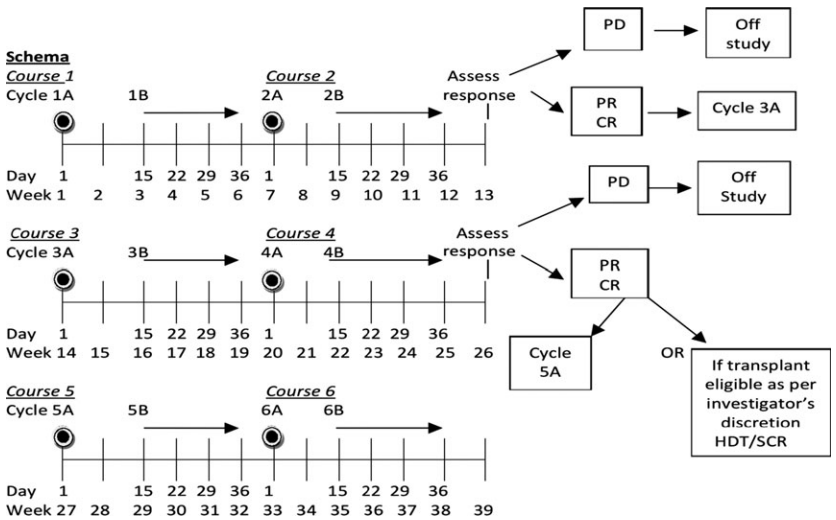

Fig 1. CEOP-P Treatment Schema Cycle (A) cyclophosphamide 750 mg/m^2 day 1 IV; etoposide 100 mg/m^2 days 1–3 IV (etoposide may be given PO on days 2 and 3 at double dose of 100 mg/m^2 BID); vincristine 1.4 mg/m^2 (capped at 2 mg) day 1 IV; prednisone 100 mg PO days 1–5; optional, per institutional standards, pegfilgrastim 6 mg day 4 of Week 1 of each course SQ. Cycle B: pralatrexate 30 mg/m^2 day 1 IV q week × 3; optional, per institutional standards, filgrastim (granulocyte colony-stimulating factor) 300 μg day 30 of each course SQ. Patients achieving stable disease after four courses (1,2,3,4) received two additional courses (5,6) and were then re-evaluated for response post-course 6. PD, progressive disease; CR, complete response; PR, partial remission; HDT/SCR; High Dose Therapy/Stem Cell Rescue

(Cheson, 2007), based on imaging modality used. Patients achieving a CR or partial remission (PR) were eligible for HDT/SCT after cycle 4B at physician discretion. Patients were followed until date of disease progression and/or death at 100 days and 2 years post consolidation of therapy.

Statistical plan

The CR rate with CHOP has been variable and reported to be in the 30-73% range depending on the subtype of PTCL (Reimer *et al*, 2009; Simon *et al*, 2010; Abouyabis *et al*, 2011). The primary statistical aim of the present study was to improve the CR rate from 40% to 63% with CEOP-P and HDT/SCT. Secondary objectives included assessment of progression-free survival (PFS), OS and toxicity of the regimen. PFS was defined as time from the first therapy until relapse, progression, or death from any cause. OS was defined as time from the first chemotherapy administered on trial until death from any cause. A two-stage Simon design (alpha = 0·10, 90% power) tested the null hypothesis that the CR rate would be greater than 40%. For the first stage of 20 evaluable patients, the trial would be terminated if 8 or fewer experienced a CR after course 2 of chemotherapy. For the second stage, a total of 34 patients were required with at least 17 patients achieving a CR at the end of therapy to consider the regimen useful.

All patients who received at least 2 complete courses of chemotherapy were evaluable for the response endpoint. Patients taken off study due to a global deterioration of health status without objective evidence of disease progression were counted as progressive disease (PD). Effort was made to document the objective progression even after discontinuation of treatment. Deaths were counted as treatment failure. CR rate was reported at the end of the CEOP-P (6 courses for patients not receiving transplant and 4–6 courses for patients receiving transplant). All eligible patients receiving at least one cycle of chemotherapy were evaluable for toxicity. All evaluable patients irrespective of the total number of cycles of therapy received were included in PFS and OS analyses.

Results

Thirty-four patients were enrolled and one withdrew consent before starting therapy, leaving 33 patients enrolled between July 2011 and January 2013. Characteristics are shown in Table I. The median age was 62 (range, 27–83) years. Twenty-one patients (64%) had PTCL, 8 (24%) AITL and 4 (12%) ALK-negative ALCL. The majority of patients (61%) had stage IV disease and 46% a high/intermediate or high risk IPI. The median number of chemotherapy cycles was 4 (range 1–6). Six patients received only 1 cycle due to either early PD (n = 4) or adverse events (n = 2). The number of patients receiving 4, 5 and 6 cycles was 9, 4 and 4, respectively.

Toxicity

Toxicities during CEOP-P were moderate. The most frequent grade 3–4 toxicities seen in ≥10% of patients and attributed to therapy included; anaemia (27%), thrombocytopenia (12%), febrile neutropenia (18%), mucositis (18%), sepsis

Table I. Patient characteristics.

Variables	*N* (%)
N	33
Median age, years (range)	62 (27–83)
Sex	
Female	9 (27)
Male	24 (73)
Karnofsky performance score	
70	5 (15)
80–100	28 (85)
Diagnosis	
PTCL-NOS	21 (64)
AITL	8 (24)
ALCL, T- and null cell types	4 (12)
Ann Arbor Stage	
II	4 (12)
III	9 (27)
IV	20 (61)
B symptoms	
No	18 (55)
Yes	15 (45)
IPI Score	
Low	9 (27)
Low – intermediate	9 (27)
High – intermediate	9 (27)
High	6 (19)
Lactate dehydrogenase	
Normal	17 (52)
Elevated	16 (48)
Extranodal involvement	
0–1	24 (73)
2 or more	9 (27)
Median number of chemotherapy cycles (range)	4 (1-6)
Median follow-up of survivors, months (range)	20·4 (11·9 – 31·2)

PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL,anaplastic large cell lymphoma; IPI, International Prognostic Index.

(15%), elevated creatinine (12%) and liver transaminases (12%). These were largely reversible with supportive care and treatment delay. Two patients discontinued treatment due to adverse events.

Response

At the end of stage 1, 10 of 20 patients (50%) achieved a CR; therefore accrual proceeded, per protocol design, to stage 2. At the end of study, the overall response rate (ORR) was 70% with 17 patients (52%) achieving a CR. At a overall median follow up of 20 months, the estimated 1- and 2-year PFS/OS rates were 48% (95% CI 31-64)/39% (95% CI 21-57), and 67% (95% CI 48-80)/60% (95% CI 39-76), respectively (Table II; Fig 2A, B). Table III shows response rates by histological subtypes, IPI and for patients treated with versus without HDT/SCT. The ORR/CR for PTCL-NOS, AITL and ALCL were 76%/48%, 38%/25% and 100%/75% respectively.

Table II. Primary and secondary outcomes.

Outcomes	*N* (%)
Best response	
CR	17 (52)
PR	6 (18)
PD	8 (24)
SD	2 (6)
Proceeded to HDT/SCT	
No	18 (55)
Yes	15 (45)
Probability	
Progression-free survival	
100 days	82 (95% CI, 64–91)
6 months	67 (95% CI, 48–80)
1 year	48 (95% CI, 31–64)
2 years	39 (95% CI, 21–57)
Overall survival	
100 days	91 (95% CI, 74–97)
6 months	82 (95% CI, 64–91)
1 year	67 (95& CI, 48–80)
2 years	60 (95% CI, 39–76)

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; HDT/SCT, high dose therapy/stem cell transplantation.

Fifteen patients (12 CR, 2 PR, 1 stable disease) received consolidation with HDT/SCT and have sustained complete remissions post-transplantation. With a median follow-up of 21·5 months, the estimated 2-year OS and PFS was 80% (95% CI 37–95) and 64% (95% CI 25–86), respectively. The PFS and OS were significantly better in these patients compared to those who did not receive HDT/SCT. The latter group had an estimated 2-year PFS of 17% (95% CI 4–36) and an OS of 44% (95% CI 22–65) (Fig 3A, B). Characteristics of patients treated versus those not treated with HDT/SCT are shown in Table IV. Patients who proceeded to SCT were younger (58 vs. 64 years) but other characteristics did not differ. On exploratory bivariate analyses, age <60 years, absence of B symptoms, low IPI score (0,1), achieving a CR and receiving a HDT/SCT were the strongest predictors associated with better PFS (Table V). For OS, lack of B symptoms, low IPI score, achieving a CR and receiving a SCT were significant. In a comparison of patients in a CR with (n = 12) or with out HDT/SCT (n = 5), both PFS and OS were similar (P = 0·26).

Overall there were 12 deaths, due to disease progression (n = 6), sepsis (n = 3), congestive heart failure (n = 1), renal failure (n = 1) and subdural haematoma (n = 1).

Discussion

In the absence of randomized clinical trials, CHOP or CHOP-like chemotherapy is considered a standard therapy for PTCLs but typically has disappointing outcomes (Savage *et al*, 2004; Vose *et al*, 2008). The advantage of a CHOP

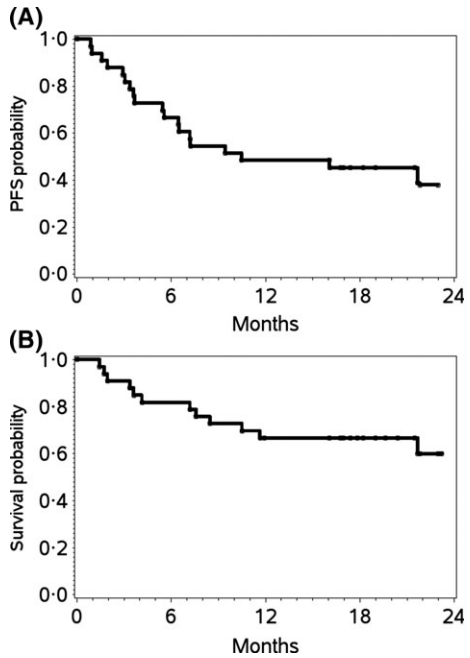

Fig 2. Progression-free survival and overall survival. (A) Kaplan–Meier curves for estimated 1- and 2-year progression-free survival: 48% [95% confidence interval (CI) 31–64] and 39% (95% CI 21–57) respectively. B. Kaplan–Meier curves for estimated 1- and 2-year overall survival: 67% (95% CI 48–80) and 60% (95% CI 39–76) respectively.

Table III. Overall complete remission rates according to risk factors.

Variables	CR *N* (%)	CR + PR (ORR) *N* (%)
Diagnosis		
PTCL-NOS	12/21 (48)	16/21 (76)
AITL, lymphoma	2/8 (25)	3/8 (38)
ALCL, T- and null cell types	3/4 (75)	4/4 (100)
IPI Score		
Low	8/9 (89)	9/9 (100)
Low – intermediate	3/9 (33)	5/9 (56)
High – intermediate	4/9 (44)	5/9 (56)
High	2/6 (33)	4/6 (67)
Auto – Transplant		
No	5/18 (28)	9/18 (50)
Yes	12/15 (80)	14/15 (93)

CR, complete remission; PR, partial remission; ORR, overall response rate; PTCL-NOS, Peripheral T-cell lymphoma, not otherwise specified; AITL, Angioimmuno-blastic T-cell lymphoma; ALCL, Anaplastic large cell lymphoma; IPI, International Prognostic Index.

'like' regimen is that it is widely used in the community setting where most patients are treated. Data from the Vancouver Cancer Agency suggested that similar outcomes were obtained when etoposide was substituted for doxorubicn (adriamycin) in DLBCL patients who were unable to receive anthracyclines due to a variety of reasons (Moccia *et al*, 2009). In order to develop a non-anthracycline platform, we substituted etoposide for doxorubicn in part A of the regimen. Etoposide has commonly been used in other regimens for PTCL, such as cisplatinum, etoposide, gemcitabine and solumedrol (PEGS), CHOEP and steroids, methotrexate, Ifosfamide, lasparaginase and etoposide (SMILE) with activity in haemophagocytic syndromes, which is often seen in patients with aggressive PTCL (Pfreundschuh *et al*, 2008; Yamaguchi *et al*, 2011; Mahadevan *et al*, 2013). Furthermore, the addition of etoposide to CHOP improves EFS in younger PTCL patients, as discussed above. Thus, the CEOP backbone was considered both rational and promising. When the study design was conceived, pralatrexate, a novel anti-folate, was the only FDA-approved drug for relapsed and refractory PTCL. The overall response rate per International Workshop Criteria (IWC) by independent central review was 29% ($n = 32$) across a variety of PTCL subtypes (O'Connor *et al*, 2011). We hypothesized that adding pralatrexate, as a non-cross resistant agent, to a predictable backbone in the front line setting might be beneficial. Our regimen sequenced pralatrexate with CEOP to avoid overlapping toxicity. Unlike other front line studies in PTCL in the

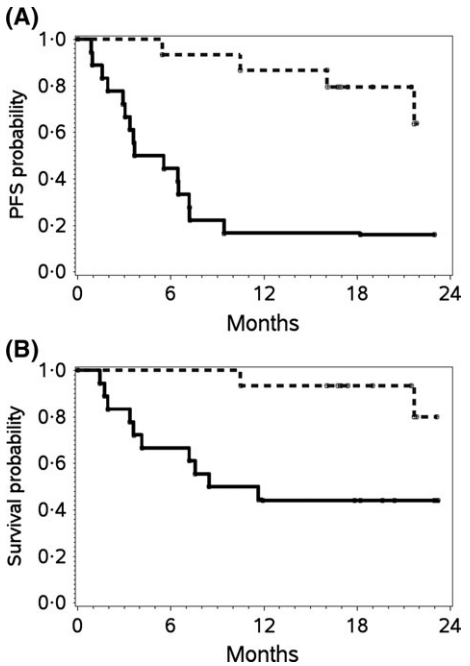

Fig 3. Progression-free survival and overall survival in patients who received HDT/SCT compared to those who did not (A) Kaplan–Meier curves at 24 months for patients treated with high dose therapy and stem cell transplantation (HDT/SCT) ($n = 15$) and without HDT/SCT ($n = 18$): progression-free survival with HDT/SCT: 63% [95% confidence interval (CI) 25–86] and without HDT/SCT: 17% (95% CI 4–36) log rank P-value = 0.0002. B. Kaplan–Meier curves at 24 months for patients treated with high dose therapy and stem cell transplantation (HDT/SCT) ($n = 15$) and without HDT/SCT ($n = 18$): Overall survival with HDT/SCT: 80% (95% CI 37–95) and without HDT/SCT: 44% (95% CI 22–65) log rank P-value = 0.007.

Table IV. Comparison of patients who did receive HDT/SCT to those who did not.

Variable	No HDT/SCT $N = 18$ N (%)	Received HDT/SCT $N = 15$ N (%)	P-value
Median age, years (range)	68 (34-83)	59 (27-69)	0·03
Age at diagnosis			
≤60 years	5 (28)	9 (60)	0·06
>60 years	13 (72)	6 (40)	
Sex			
Female	4 (22)	5 (33)	0·48
Male	14 (78)	10 (67)	
Karnofsky performance score			
70	3 (17)	2 (13)	0·79
80–100	15 (83)	13 (87)	
Diagnosis			
PTCL-NOS	10 (56)	11 (73)	0·64
AITL,	5 (28)	3 (20)	
ALCL, T- and null cell types	3 (17)	1 (7)	
Ann Arbor Stage			
II	2 (11)	2 (13)	0·84
III–IV	16 (89)	13 (87)	
B symptoms			
No	9 (50)	9 (60)	0·57
Yes	9 (50)	6 (40)	
IPI Score			
Low	4 (22)	5 (33)	0·65
Low – intermediate	4 (22)	5 (33)	
High – intermediate	6 (33)	3 (20)	
High	4 (22)	2 (13)	
Lactate dehydrogenase			
Normal	9 (50)	8 (53)	0·85
Elevated	9 (50)	7 (47)	
Extranodal involvement			
0–1	12 (67)	12 (80)	0·39
2 or more	6 (33)	3 (20)	
Median number of chemotherapy cycles (range)	2 (1–6)	4 (1–6)	0·03

HDT/SCT, high dose therapy and stem cell transplantation, PTCL, peripheral T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; IPI, International Prognostic Index.

US which have often taken >3–5 years to complete, our T Cell Consortium study accrued rapidly in 1·5 years, suggesting that novel strategies for this rare disease can be tested in a reasonable time frame with committed investigators. The frequency of neutropenia and thrombocytopenia was not significantly increased compared to historical data with CHOEP (Schmitz *et al*, 2010). While our interim analysis showed that CEOP-P met the pre-defined stage 1 response criteria with a CR rate of 52% compared with 31% reported in prospective studies with CHOP (Reimer *et al*, 2009), the

Table V. Probability of 2 year PFS and OS according to risk factors.

Variable	PFS (95% CI)	P-value	OS (95% CI)	P-value
Age at diagnosis				
≤60 years	71 (41–88)	0·007	78 (47–92)	0·14
>60 years	17 (4–40)		48 (22–70)	
Sex				
Female	56 (20–80)	0·53	78 (36–94)	0·33
Male	33 (14–54)		53 (29–73)	
Karnofsky performance score				
70	0	0·10	40 (5–75)	0·10
80–100	43 (22–62)		63 (39–80)	
Diagnosis				
PTCL-NOS ($n = 21$)	39 (14-64)	0·31	59 (29–80)	0·62
AITL ($n = 8$)	25 (4-56)		50 (15–77)	
ALCL, T- and null cell types ($n = 4$)	50 (6-84)		75 (13–96)	
Ann Arbor Stage				
II	75 (13-96)	0·16	100	0·26
III	44 (7-78)		52 (8–84)	
IV	29 (11-50)		55 (31–73)	
B symptoms				
No	44 (18-68)	0·16	71 (37–89)	0·04
Yes	32 (11–56)		47 (21–69)	
IPI Score				
Low ($n = 9$)	88 (43–98)	0·01	100	0·007
Low – intermediate ($n = 9$)	44 (14–72)		78 (36–94)	
High – intermediate (n =9)	11 (1–39)		22 (3–51)	
High ($n = 9$)	0		50 (11–80)	
Lactate dehydrogenase				
Normal	59 (32-78)	0·11	82 (55-94)	0·03
Elevated	15 (1-44)		33 (8-63)	
Extranodal involvement				
0–1	50 (26–70)	0·05	66 (38-83)	0·21
2 or more	0		44 (13-72)	
Best response				
CR	70 (36–89)	<0·0001	70 (36–89)	0·01
PR	17 (1–52)		83 (27–97)	
PD	0		25 (4–56)	
SD	0		50 (1–91)	
Autologous Transplant				
No ($n = 18$)	17 (4–36)	0·0002	44 (22–65)	0·007
Yes ($n = 15$)	66 (26-88)		80 (37–95)	

PFS, progression free survival; OS, overall survival; 95% CI, 95% confidence interval; PTCL, Peripheral T-cell lymphoma; AITL, Angioimmunoblastic T-cell lymphoma; ALCL, Anaplastic large cell lymphoma; IPI, International Prognostic Index; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

2-year PFS and OS of 39% and 60%, respectively, do not appear to be a significant improvement over historic outcomes reported with CHOP-like regimens. It is plausible

that, in our study, pralatrexate alone between the CEOP doses may actually have decreased the intensity of treatment and hence the overall efficacy.

Intensifying upfront therapy with HDT/SCT may improve the generally poor outcomes seen with standard CHOP induction chemotherapy; however, the major limitation is that significant subsets of patients never manifest sufficient chemosensitivity in order to undergo consolidative HDT/SCT. Recent prospective trials assessing the role of consolidative HDT/SCT in patients achieving a CR/PR, report that only 66–72% of enrolled patients actually receive the planned HDT/SCT (Reimer *et al*, 2009; d'Amore *et al*, 2012). Despite these limitations, cumulatively these prospective studies suggest a moderately better PFS and OS than population-based series with CHOP (Ellin *et al*, 2014). In our study, patients who received HDT/SCT had improved outcomes when compared to patients who did not, which reflects the poor prognosis of patients who are chemo-refractory and do not receive HDT/SCT. Younger patients and those with a low IPI did particularly well. Interestingly, within the caveats of small sample size, no statistically significant difference in PFS and OS was noted in patients who achieved a CR and proceeded to HDT/SCT *versus* those with a CR and no HDT/SCT. This is similar to results from a retrospective review in which the most dominant prognostic factor was response to initial therapy (CR versus other), with no OS difference based on choice of upfront regimen or SCT in first remission (Abramson *et al*, 2014). Unfortunately, all transplant studies have similar limitations due to selection biases with a tendency to include mainly younger patients with chemosensitive disease and exclude frail patients who are unable to tolerate HDT (Pedersen *et al*, 2014). Therefore, the question still remains whether or not the HDT/SCT as consolidation after primary therapy improves outcome. Randomized studies comparing chemotherapy to chemotherapy with HDT/SCT are unfortunately lacking.

Many studies have investigated combining novel treatment regimens with CHOP as the backbone chemotherapy in PTCL. Thus far, none have demonstrated a significant improvement in outcomes when compared to CHOP alone. As serum concentration of VEGF has been shown to be an independent predictor of poor outcome in patients with NHL (Salven *et al*, 1998), the Eastern Cooperative Oncology Group (ECOG) 2404 trial evaluated the combination of an antiangiogenic agent bevacizumab (Avastin) and CHOP (ACHOP) followed by maintenance bevacizumab (Salven *et al*, 1998). Despite a high CR rate, the 1-year PFS was only 44% at a median follow-up of 3 years and the combination was quite toxic, with grade 3 congestive heart failure reported in 18% of patients (Advani *et al*, 2012; Ganjoo *et al*, 2014). Combinations of bortezomib/CHOP, alemtuzamab/CHOP or CHOEP and denileukin difitox/CHOP have also been evaluated and results do not report durable responses (Enblad *et al*, 2004; Gallamini *et al*, 2007; Kim *et al*, 2012; Binder *et al*, 2013; Foss *et al*, 2013).

The Southwestern Oncology Group (SWOG) 0350 trial evaluated PEGS, a novel non-CHOP regimen, based on the premise that the poor efficacy of CHOP therapy may be due to T cells expressing high levels of p-glycoprotein, resulting in MDR (Mahadevan *et al*, 2013). Although the heterogeneous patient population, which included relapsed disease, confounded the intended interpretation, the 2-year PFS of 12% with an ORR of 31% to frontline treatment was disappointing. A UK group is currently evaluating another gemcitabine-based regimen in combination with cisplatin (GEM-P) versus CHOP in a randomized phase 2 study (NCT01719835).

Since our study inception, several other novel agents have been approved for relapsed PTCL (Pro *et al*, 2012; Dupuis *et al*, 2014; Lee *et al*, 2015). The encouraging single agent activity of brentuximab vedotin in relapsed and refractory ALCL (Pro *et al*, 2012), as well as in other PTCLs (Horwitz *et al*, 2014), has led to its evaluation in combination with CHOP (Fanale *et al*, 2014). The latter study has shown promising phase 1 results and a phase 3 study comparing brentuximab vedotin with modified CHOP (without vincristine) versus CHOP (ECHELON-2) is ongoing in patients with CD30 + PTCL (NCT 01777152). Romidepsin and Belinostat are histone deacetylase inhibitors, approved for relapsed PTCL with activity across multiple subtypes (Coiffier *et al*, 2012; Lee *et al*, 2015). Romidepsin has been evaluated in combination with CHOP in the front line setting with an ORR/CR of 68% and 51%, respectively. With a median follow-up of 17·5 months, the estimated PFS is 57% at 18 months (Dupuis *et al*, 2014). This combination is also being tested in a randomized phase 3 trial (NCT01796002).

Recent studies have identified molecular subsets with improved prognostication among PTCL-NOS, ALK-positive and ALK-negative lymphomas (Iqbal *et al*, 2010; Piccaluga *et al*, 2013; Parrilla Castellar *et al*, 2014). Additional mutations (i.e. *TET2* and *RHOA*) have been identified in AITL. These advances provide a rationale for the development of novel pathway targeted regimens that specifically target distinct subsets of PTCL (Cairns *et al*, 2012; Sakata-Yanagimoto *et al*, 2014).

In conclusion, the sequential addition of pralatrexate to a CEOP backbone did not demonstrate sufficient activity to warrant further exploration. It is unclear whether a different schedule that would not de-intensify chemotherapy may be superior. The overall management of front-line PTCL remains challenging, and currently there is no "home run" in any front line therapeutic approach. Clearly, investigating additional novel approaches is critical and defining the optimal front line therapy in PTCL continues to be a challenge and an unmet need.

Acknowledgements

This study was supported by Allos Therapeutics/Spectrum Pharmaceuticals Inc.

Author contributions

Ranjana Advani designed the research study, enrolled patients, analysed data, and wrote the manuscript. Stephen Ansell, Mary Jo Lechowicz, Anne Beaven, Ken Carson, Andrew Evens and Julie Vose designed the research study, enrolled patients and critically revised manuscript. Fausto Loberiza designed the research study, analysed data and critically revised the manuscript. Francine Foss, Steven Horwitz, Barbara Pro, Lauren Pinter Brown, Sonali Smith, Andrei Shustov and Kerry Savage designed the research study and critically revised manuscript. All authors approved the final version of the paper for publication.

Conflicts of interest

RHA has reported research funding from Seattle Genetics and Allos Therapeutics. MJL has reported research funding from Allos Therapeutics, Celgene, Seattle Genetics and Millennium; consultancy for Millennium, Allos Therapeutics and Seattle Genetics. AB has reported GlaxoSmithKline (GSK) stock and family member is an employee of GSK; research funding from Spectrum Pharmaceuticals; speakers board for Celgene and Seattle Genetics. KC has reported research funding and honoraria from Spectrum Pharmaceuticals. FF has reported research funding from Merck, Spectrum Pharmaceuticals, Celgene and Seattle Genetics; membership on Board of Directors or advisory committees for Eisai and Millennium; honoraria received from Celgene and Millennium. SH has reported research funding from Celgene, Spectrum Pharamaceuticals, Genzyme, Seattle Genetics, Janssen and Millennium; Consultancy for Spectrum Pharamaceuticals, Celgene, Seattle Genetics, Kyowa Hakko Kirn Pharma, Infinity Pharmaceuticals and Millennium. BP has reported honoraria from Spectrum Pharmaceuticals. LPB has reported consultancy/honoraria from Spectrum Pharmaceuticals. SMS has reported consultancy for Allos Therapeutics, Celgene, Seattle Genetics, Onyx, Genentech, Micromet and Gilead; speakers bureau for Janssen. AS has reported research funding from Celgene; consultancy honoraria from Celgene and Spectrum Pharamaceuticals. KJS has reported research funding from Spectrum Pharmaceuticals. JV has reported research funding from Spectrum Pharmaceuticals. All remaining authors have declared no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Dose modifications for hematological toxicities.

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