ARTICLE

Dose-adjusted EPOCH chemotherapy for untreated peripheral T-cell lymphomas: a multicenter phase II trial of West-JHOG PTCL0707

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Haematologica 2017
Volume 102(12):2097-2103

ABSTRACT

The standard CHOP therapy for peripheral T-cell lymphoma has resulted in unsatisfactory outcomes and it is still not clear what is the optimal front-line therapy. We conducted a multicenter phase II study of dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone (EPOCH) for untreated peripheral T-cell lymphoma patients. In this prospective study, 41 patients were treated with dose-adjusted-EPOCH as initial therapy: peripheral T-cell lymphoma-not otherwise specified, n=21; angioimmunoblastic T-cell lymphoma, n=17; anaplastic lymphoma kinase-positive anaplastic large cell lymphoma, n=2; and anaplastic lymphoma kinase-negative anaplastic large cell lymphoma, n=1. Median patient age was 64 years (range: 32-79 years). According to the International Prognostic Index criteria, 51.2% were at high-intermediate or high risk. The overall response and complete response rates were 78.0% [95% confidence interval (CI): 62.4-89.4%] and 61.0% (95%CI: 44.5-75.8%), respectively. At the median follow up of 24.0 months, the 2-year progression-free survival and overall survival were 53.3% (95%CI: 36.4-67.5%) and 73.2% (95%CI: 56.8-84.1%), respectively. The younger patients (≤ 60 years old) had a high response rate (overall response 94.1% and complete response 70.6%) and survival rate (progression-free survival 62.5% and overall survival 82.4%). The most common grade ≥ 3 adverse events were neutropenia (74.5%), anemia (40.8%), thrombocytopenia (22.0%), and febrile neutropenia (9.0%). Dose-adjusted-EPOCH had a high response rate with a tolerable toxicity profile. Our results indicate that dose-adjusted-EPOCH is a reasonable first-line approach for peripheral T-cell lymphoma patients and may improve outcomes. (*UMIN trial registration number: UMIN000000829*).

Introduction

Peripheral T-cell lymphomas (PTCLs) are rare, heterogeneous diseases that comprise 10-15% of all adult non-Hodgkin lymphoma (NHL) cases. PTCLs have been classified into four groups according to the World Health Organization (WHO) classification sys-

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Received: March 10, 2017.
Accepted: September 20, 2017.
Pre-published: September 29, 2017.

doi:10.3324/haematol.2017.167742

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/102/12/2097

tem (2008), and the most common subtypes are nodal T-cell lymphomas, PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), and ALK-negative ALCL.[1]

There is no standard therapy for PTCLs; CHOP therapy (cyclophosphamide, prednisone, vincristine, and hydroxyl doxorubicin) is the most widely used, but overall survival (OS) is poor.[2,3] In a systematic review and meta-analysis of 2815 patients with PTCL, treatment with CHOP or CHOP-like regimens produced a complete response (CR) in 44-64% of PTCL-NOS and in 36-70% of AITL patients, although ALK-positive ALCL had a higher CR rate than other T-cell lymphomas.[2] Disease progression during chemotherapy occurred in 30-40% of the patients and durable remissions after CHOP alone are not common. In the PTCL-NOS patients treated primarily with CHOP at the British Columbia Cancer Agency, the 5-year progression-free survival (PFS) and OS were only 29% and 35%, respectively.[4] Patients with ALK-negative ALCL and AITL had similar 5-year OS, of 34% and 36%, respectively. Given the poor outcomes of PTCL patients, several studies are investigating the role of high-dose chemotherapy and autologous stem cell transplantation in the upfront setting; however, the benefits in terms of preventing relapse are still a subject of debate.[5-8]

The addition of etoposide to CHOP-based regimens improved the CR in PTCL in some studies.[9,11] The German High-grade Non-Hodgkin Lymphoma Study Group (DSHNHL) assessed 320 patients from eight prospective trials and reported that patients who were young adults (< 60 years) with normal lactate dehydrogenase (LDH) had a significantly improved outcome with CHOP plus etoposide (CHOEP) *versus* CHOP alone.[3] A dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab regimen had excellent outcomes in primary mediastinal B-cell lymphoma, germinal center B-cell diffuse large B-cell lymphoma, and Burkitt lymphoma.[12-14] Recently, Dunleavy *et al.* reported the encouraging results of a phase II trial of dose-adjusted EPOCH in 24 patients with untreated ALK-positive (n=15) and ALK-negative (n=9) ALCL.[15] The event-free survival (EFS) in ALK-positive and ALK-negative ALCL was 72.0% and 62.5%, respectively, and the OS was 78.0% and 87.5% at a median potential follow up of 14.4 years. Based on the hypothesis that dose-adjusted EPOCH may improve treatment outcome, we undertook a phase II prospective study of dose-adjusted EPOCH in patients with nodal PTCL.

Methods

The study prospectively enrolled 41 consecutive patients with untreated PTCL from September 2007 to October 2011. The study population was made up of nodal PTCLs, i.e. PTCL-NOS, AITL, ALK-positive ALCL, and ALK-negative ALCL. Diagnoses were based on the WHO classification. All patients were confirmed to be human T-cell lymphotropic virus type 1 (HTLV-1) negative. The pathology was reviewed by hematopathologists (TYo, SN, and KO) to confirm the diagnoses. All patients gave written informed consent. This study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the institutional review boards of Okayama University Hospital, Shikoku Cancer Center, Japanese Red Cross Society Himeji Hospital, Kaneda Hospital, Kanazawa Medical University Hospital, Okayama

Table 1. Patients' characteristics.

Characteristic	Number of patients (%)
Total patients	41 (100)
Sex	
Male	21 (51.2)
Female	20 (48.8)
Age	
Median (range), years	64 (32-79)
≤ 60	17 (41.5)
> 60	24 (58.5)
Performance status	
ECOG 0 to 1	35 (85.4)
ECOG 2	6 (14.6)
B symptoms	
No	20 (48.8)
Yes	21 (51.2)
Clinical stage	
I/II	8 (19.5)
III/IV	33 (80.5)
LDH level	
Normal	13 (31.7)
Above normal	28 (68.3)
Extranodal sites	
0 to 1	37 (90.2)
> 2	4 (9.8)
BM involvement	
No	13 (31.7)
Yes	28 (68.3)
Soluble IL-2 receptor	
Under median	17 (48.6)
Over median	18 (51.4)
Pathology	
PTCL-NOS	21 (51.2)
AITL	17 (41.5)
ALK (+) ALCL	2 (4.9)
ALK (-) ALCL	1 (2.4)
IPI score	
Low (0 to 1)	10 (24.4)
Low intermediate (2)	10 (24.4)
High intermediate (3)	16 (39.0)
High (4 to 5)	5 (12.2)
PIT group	
Group 1 (0)	5 (12.2)
Group 2 (1)	9 (22.0)
Group 3 (2)	20 (48.8)
Group 4 (3 to 4)	7 (17.0)
Dose escalation	
No	17 (41.5)
Yes	24 (58.5)

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; BM: bone marrow; PTCL-NOS: peripheral T-cell lymphomas-not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma; IPI: International Prognostic Index; PIT: prognostic index for T-cell lymphoma.

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Chemotherapy and dose adjustments

The dose-adjusted EPOCH starting doses were doxorubicin 10 mg/m^2, etoposide 50 mg/m^2, and vincristine 0.4 mg/m^2 daily as a continuous infusion over days 1 to 4 (96 hours in total); cyclophosphamide 750 mg/m^2 as a 2-hour infusion on day (d)5; and prednisone 60 mg/m^2 on d1 to d5, as previously described.[16] Patients received granulocyte colony-stimulating factor (G-CSF) on d6 until the ANC was more than 5.0x10^9 cells/L past the nadir. Fluconazole and sulfamethoxazole/trimethoprim were prophylactically administered according to the risk of infection in each patient. Twice-weekly complete blood counts were obtained three days apart and the doses of etoposide, doxorubicin, and cyclophosphamide were adjusted every subsequent cycle based on the neutrophil nadir. If the ANC nadir was 0.5x10^9 cells/L or over, doses were increased by 20% from those of the previous cycle. If the nadir ANC was less than 0.5x10^9 cells/L continued for one or two monitoring points, the doses were not changed. If the nadir ANC was less than 0.5x10^9 cells/L continued for at least three monitoring points or the platelet nadir was less than 25.0x10^9 cells/L, the doses were reduced by 20% from those of the previous cycle. If patients younger than 70 years of age had a dose reduction below the starting-dose level, only cyclophosphamide was reduced by 20%. If the patient was 70 years old or older, the starting doses were reduced by 20%. Vincristine was reduced by 25% or 50% for grade 2 or 3 motor neuropathy, respectively, and by 50% for grade 3 sensory neuropathy. The sites of disease were restaged after cycle 2 and every 2 cycles thereafter. The cycles were repeated every three weeks, and patients received at least 2 cycles beyond CR, for a minimum of 6 and a maximum of 8 cycles.

Primary end point

The primary end point was patient response rate, and secondary end points were the safety of the treatment, OS, and PFS. Tumor responses were evaluated with computer-assisted tomography scan according to the International Workshop criteria[17] and were classified as CR, unconfirmed CR (uCR), or partial response (PR).

Sample size estimation

Using historical control data,[2] we assumed that the lower limit of interest was 40% and the expected response rate was 60%. Under these assumptions, 38 patients needed to be recruited for an α error of 0.05 and power of 80%. After considering patient loss as a result of dropout, we set the target number of patients to 42. The current study had enrolled 41 without drop out; therefore, it was over required sample size (n=38).

Statistical analysis

The PFS and OS were estimated using the Kaplan-Meier method and statistical differences among the curves were evaluated with the log rank test. The ability of the following clinical variables to predict outcome was evaluated in univariate analyses: sex, age, performance status (PS), B symptoms, clinical stage, LDH level, extranodal involvement, bone marrow involvement, soluble interleukin (IL)-2 receptor, pathology, IPI, prognostic index for prognostic index for T-cell lymphoma (PIT), and dose escalation. The significance of these variables was also evaluated in a multivariate analysis using a stepwise Cox regression model. All reported *P*-values are two-sided; $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed using STATA software (v.12; StataCorp, College Station, TX, USA).

Results

Patients' characteristics

The histological diagnoses were reviewed by a panel of expert hematopathologists and 41 patients with untreated PTCL were included in the analysis of toxicity and response. Patients' characteristics are summarized in Table 1. Median patient age was 64 years (range: 32-79 years) and more than half of the patients were older than 60; 9 patients (22.0%) were over 70. PTCL-NOS was the predominant histological finding (n=21, 51.2%), followed by AITL (n=17, 41.5%), ALK-positive ALCL (n=2, 4.9%), and ALK-negative ALCL (n=1, 2.4%). The majority of the patients were stage III and IV. According to IPI criteria, 51.2% were at high-intermediate or high risk. Twenty-seven patients (65.9%) were categorized as PIT Group 3-4.

Response to treatment

Of the 41 patients assessed, 61.0% had a CR [95% confidence interval (CI): 44.5-75.9%] and 17.0% had a PR (95%CI: 7.2-32.1%) to dose-adjusted EPOCH treatment. The overall response rate (ORR) was 78.0% (95%CI: 62.4-89.4%). In patients with PTCL-NOS, the ORR and

Table 2. Adverse event of dose-adjusted-EPOCH treatment (total 255 cycles).

Adverse event	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	8.2	16.5	58.0
Thrombocytopenia	16.5	15.3	6.7
Anemia	37.3	40.4	0.4
AST/ALT elevation	4.3	0	0
ALP elevation	3.9	0	0
Creatinine elevation	0.8	0	0
Febrile neutropenia	0	9.0	0
Neuropathy	3.5	0.8	0
Infection	0	3.1	0.4
Constipation	3.1	0	0
Headache	3.1	0	0
Nausea	1.6	0	0
Mucositis	1.2	1.6	0

CR were 71.4% (95%CI: 47.8-88.7%) and 47.6% (95%CI: 25.7-70.2%), respectively. In AITL patients, ORR and CR were 82.4% (95%CI: 56.6-96.2%) and 76.5% (95%CI: 50.1-93.2%), respectively. The univariate analysis showed that age 60 years or under was the only parameter related to a better response to therapy (ORR: *P*=0.036; CR: *P*=0.29). The younger patients (≤ 60 years old) had a high response rate (ORR 94.1%, 95%CI: 71.3-99.9% and CR 70.6%, 95%CI: 44.0-89.7%). For elderly patients (>60 years old), ORR and CR rates were 66.7% (95%CI: 44.7-84.4%) and 54.2% (95%CI: 32.8-74.4%), respectively. Histology subtype, LDH, PS, and systemic B symptoms were not significantly related to the response to therapy. Recurrence or disease progression occurred in 9 (22.0%) of the 41 patients who initially responded to chemotherapy.

Toxicity and dose adjustments

In a total of 255 cycles (median: 6 cycles) of dose-adjusted EPOCH treatment, 20% of dose escalation was performed in 60 cycles (23.5%), and 24 of all 41 patients (58.5%) experienced dose escalation (Figure 1). The patients under 70 years of age received a total of 208 cycles of dose-adjusted EPOCH treatment, and 36.1% of cycles had escalation above and 10.1% had reduction below the starting-dose level. In patients aged 70 years or older, the starting doses were reduced by 20%, and 60.9% of cycles had escalation above and 6.5% had reduction below the starting-dose level. The final dose level for each patient aged under 70 years and for those aged 70 years or older was above the full dose (100%) level in 17 of 32 patients (53.1%) and 5 of 9 patients (55.6%), respectively (Figure 1).

Toxicity data of grade ≥2 adverse events are listed in Table 2. The most common grade ≥3 adverse events were neutropenia (74.5%), anemia (40.8%), and thrombocytopenia (22.0%). Febrile neutropenia occurred in 9.0% of the total cycles. Grade 2 and 3 neuropathy occurred in 3.5% and 0.8%, respectively. Grade 3 infections occurred in 8 cycles (3.1%; 4 catheter-related infections, 2 cases of sepsis, and 2 cases of pneumonia). One patient with rheumatoid arthritis who had previously been treated with methotrexate (MTX) developed severe (grade 4) progressive multifocal leukoencephalopathy (PML) after the third cycle. Gastrointestinal toxicities were generally mild. Grade 2 constipation occurred in 3.1%. Mucositis was observed in 4.3% (grade 3: 1.6%; grade 2: 1.2%; and grade 1: 1.6%, respectively). Liver or renal toxicity was also mild; no grade 3 to 4 AST/ALT, ALP or creatinine elevation was seen. General fatigue was observed in 7.1%; however, all events were grade 1. There were no cardiac complications or treatment-related deaths.

Survival and prognostic factors

At the median follow up of 24.0 months, the 2-year PFS and OS were 53.3% (95%CI: 36.4-67.5%) and 73.2% (95%CI: 56.8-84.1%), respectively (Figure 2A). Two-year PFS and OS of younger patients (≤ 60 years old) were 62.5% (95%CI: 34.9-81.1%) and 82.4% (95%CI: 54.7-93.9%), respectively (Figure 2B). In patients with PTCL-NOS, the 2-year PFS and OS were 47.1% (95%CI: 25.1-66.4%) and 61.9% (95%CI: 38.1-78.8%) (Figure 2C and D). In AITL patients, the 2-year PFS and OS were 55.2% (95%CI: 28.1-75.7%) and 88.2% (95%CI: 60.6-96.9%) (Figure 2C and D). No statistically significant trend was observed between AITL and PTCL in 2-year OS (*P*=0.069). No patients were treated with high-dose chemotherapy and autologous stem cell transplantation in first remission. In the univariate analyses, there was a significant association with PFS in the IPI low-risk group (low + low-intermediate) *versus* IPI high-risk group (high intermediate + high), and female *versus* male patients, while there was no significant difference in OS (Table 3). In the multivariate analysis, no factors were significant predictors of either PFS or OS. In PTCL-NOS patients, there was no significant difference in PFS and OS

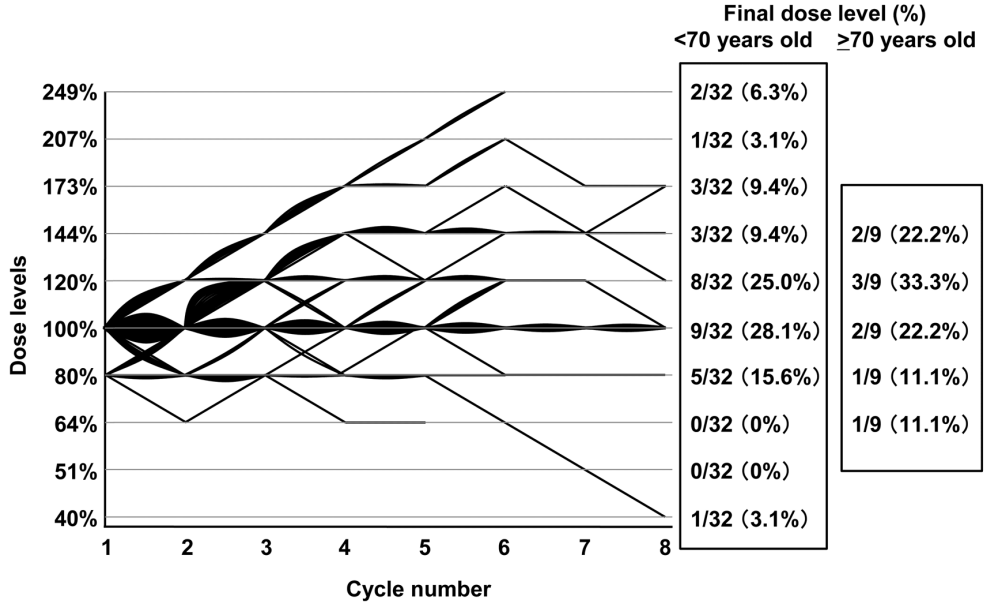

Figure 1. Map of dose levels achieved, according to cycle. Patients started with full dose (100%) EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and subsequent cycles were dose adjusted every cycle based on the previous cycle. If the patient was 70 years or older, the starting doses were reduced by 20%. (Right) Final dose level for each patient aged under 70 years of age and for those aged 70 years or older.

Table 3. Patients' outcome.

Characteristic	N (%)	% PFS at 2 years	P	%OS at 2 years	P
Total patients	41 (100)	53.3		73.2	
Sex					
Male	21 (51.2)	33.8		61.9	
Female	20 (48.8)	73.3	**0.014**	85.0	0.083
Median age, y (range)					
≤ 60	17 (41.5)	62.5		82.4	
> 60	24 (58.5)	47.1	0.254	66.7	0.322
Performance status					
ECOG 0 to 1	35 (85.4)	55.3		74.3	
ECOG 2	6 (14.6)	40.0	0.527	66.7	0.676
B symptoms					
No	20 (48.8)	57.9		85.0	
Yes	21 (51.2)	47.4	0.716	61.9	0.109
Clinical stage					
I/II	8 (19.5)	87.5		87.5	
III/IV	33 (80.5)	44.0	0.059	69.7	0.348
LDH level					
Normal	13 (31.7)	75.0		76.9	
Above normal	28 (68.3)	42.9	0.095	71.4	0.708
Extranodal sites					
0 to 1	37 (90.2)	52.0		75.7	
> 2	4 (9.8)	66.7	0.778	50.0	0.161
BM involvement					
No	13 (31.7)	51.3		76.7	
Yes	28 (68.3)	56.3	0.826	70.0	0.600
Soluble IL-2 receptor					
Under median	17 (48.6)	70.1		88.2	
Over median	18 (51.4)	42.4	0.133	61.1	0.061
Pathology					
PTCL-NOS	21 (51.2)	47.1		61.9	
AITL	17 (41.5)	55.2		88.2	
ALK (+) ALCL	2 (4.9)	100.0		50.0	
ALK (-) ALCL	1 (2.4)	100.0	0.629	100.0	0.244
IPI score					
Low (L: 0 to 1)	10 (24.4)	80.0		90.0	
Low-intermediate (LI:2)	10 (24.4)	55.6		70.0	
High-intermediate (HI:3)	16 (39.0)	33.3		68.8	
High (H: 4 to 5)	5 (12.2)	50.0	0.200	60.0	0.591
L + LI	20 (48.8)	68.4		80.0	
HI + H	21 (51.2)	37.7	**0.049**	66.7	0.348
PIT group					
Group 1 (0)	5 (12.2)	80.0		100.0	
Group 2 (1)	9 (22.0)	62.5		66.7	
Group 3 (2)	20 (48.8)	43.6		75.0	
Group 4 (3 to 4)	7 (17.0)	51.4	0.572	57.1	0.433
Group 1-2	14 (34.1)	69.2		78.6	
Group 3-4	27 (65.9)	44.5	0.211	70.4	0.575
Dose escalation					
No	17 (41.5)	55.5		76.5	
Yes	24 (58.5)	51.8	0.740	70.8	0.666

N: number; PFS: progression-free survival; OS: overall survival; y: years; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; BM: bone marrow; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma; IPI: International Prognostic Index; PIT: prognostic index for T-cell lymphoma.

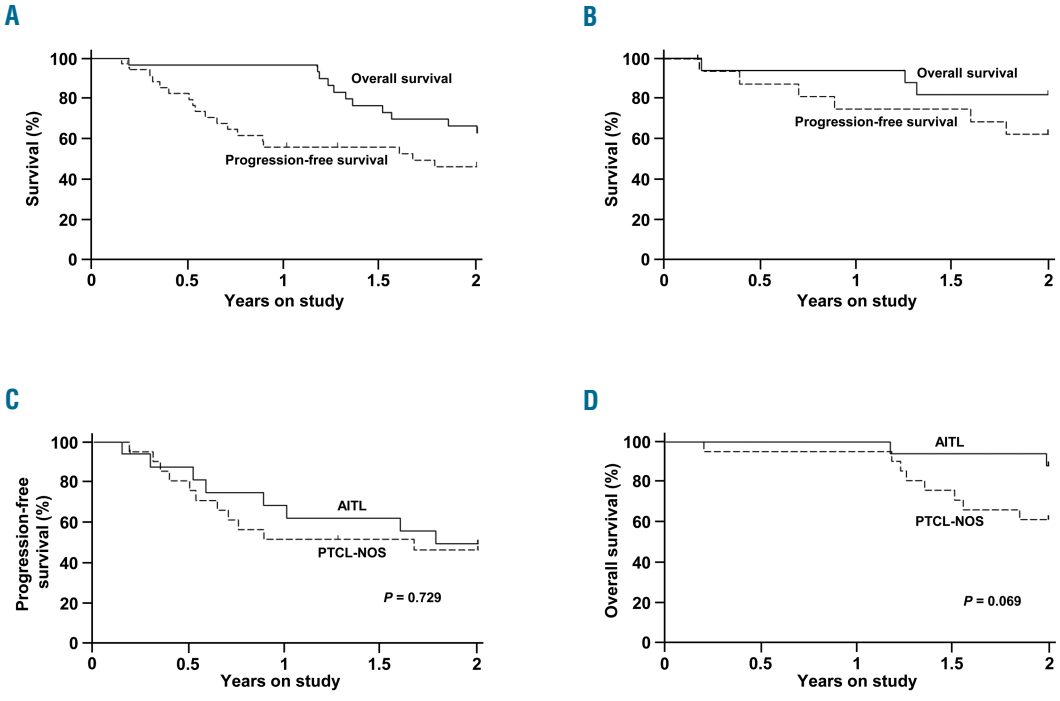

Figure 2. Kaplan-Meier estimates of progression-free and overall survival of patients with peripheral T-cell lymphomas (PTCLs) receiving dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) (DA-EPOCH). Analysis of progression-free survival (PFS) and overall survival (OS) for all patients in this study (A) and younger patients (≤ 60 years old) (B). PFS (C) and OS (D) of angioimmunoblastic T-cell lymphoma (AITL) and PTCL-not otherwise specified (PTCL-NOS) patients.

between PIT group1-2 and PIT group 3-4 (2-year PFS=55.6% *vs.* 40.0%, *P*=0.630; 2-year OS=77.8% *vs.* 50.0%, *P*=0.201). The Prognostic Index for AITL (PIAI), comprising age over 60 years, PS ≥ 2, extranodal sites >1, B symptoms, and platelet count less than $150x10^9$/L, was demonstrated to be the better risk model for AITL.[18] In patients with AITL, there was no significant difference in PFS and OS between the PIAI low-risk group (0-1 factors, n=9) and high-risk group (2-5 factors, n=8) (2-year PFS=66.7% *vs.* 29.2%, *P*=0.119; 2-year OS=100% *vs.* 75.0%, *P*=0.121).

Discussion

There is evidence for increased expression of the multidrug resistance gene (*mdr-1*) in relapsed and refractory lymphoma.[19-21] Rodriguez-Antona *et al.* reported that genomic gain was shown in *mdr-1* genes in PTCLs.[21] The EPOCH regimen was designed on the basis of *in vitro* findings that *mdr-1* tumor cells showed relatively less resistance with prolonged, low-concentration exposure to vincristine and doxorubicin than with brief higher-concentration exposure.[22,23] The dose-adjusted EPOCH regimen has yielded excellent outcomes in B-cell lymphoma and ALCL.[12-15] In the current study, the dose-adjusted EPOCH produced a high response rate in patients with nodal PTCLs. The ORR and CR rates were 78.0% and 61.0%, respectively, and the 2-year OS was 73.2%. Selection bias does not appear to account for the favorable results achieved with dose-adjusted EPOCH in the current study. More than half of the patients were older than 60 years and 27 (65.9%) patients were included in PIT Group 3-4, suggesting that more patients with aggressive disease status were treated with dose-adjusted EPOCH.

Hyper CVAD/MA (hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone/methotrexate, cytarabine) produced a better overall response rate (85%) and CR rate (80%) than CHOP-like therapy; however, there was no significant difference in 3-year OS between front-line regimens (CHOP-like 55%, hyper CVAD/MA 49%).[5] For younger patients, the addition of etoposide to CHOP improved the response rates. Kim *et al*. reported that CHOP plus etoposide and gemcitabine had an ORR of 72%, with 61% CR in 18 PTCL patients.[9] The Nordic Lymphoma Group study used biweekly CHOEP as part of an up-front high-dose chemotherapy and autologous stem cell transplantation strategy and achieved an ORR of 82%, with 51% attaining CR.[24] The DSHNHL reported that, in patients aged 60 years or younger with a normal LDH, CHOEP significantly improved the 3-year EFS (75.4% *vs.* 51.0%, *P*=0.003), although the OS was not significantly affected compared with CHOP.[3] In this study, younger patients (≤ 60 years old) had high response (ORR 94.1% and CR 70.6%) and survival (PFS 62.5% and OS 82.4%) rates. EPOCH therapy administered using a unique infusional approach plus a dose-adjustment strategy may shed new light on the treatment of PTCL. Dose-adjusted EPOCH had an encouraging survival curve (2-year OS=70.4%) even in PIT Group 3-4, and longer follow up may demonstrate a more robust survival benefit as first-line treatment in younger PTCL patients. Unlike in younger patients, the addition of etoposide to CHOP in older patients seemed to result in inappropriately high toxicity and did not improve the outcome, although the patient numbers were too small to be compared in the DSHNHL

analysis.[3] Wilson *et al*. adopted a dose-adjustment strategy based on the hematopoietic nadir, because pharmacokinetic analyses of etoposide and doxorubicin had showed significant interpatient variation in steady-state plasma concentrations.[16,25] In this study, we also adopted a dose-adjustment strategy. The starting doses were reduced by 20% in patients aged 70 years or older and 60.9% of cycles had escalation above. In previously reported prospective studies of dose-adjusted EPOCH, dose escalation could also be conducted according to the protocols even in elderly patients (around 50%[13,16]); figures which are compatible with our study. For elderly patients (> 60 years old), the ORR and CR rates were 66.7% and 54.2%, respectively. Elderly patients (> 60 years old) had significantly worse response rates than younger patients (≤ 60 years old), while there was no significant difference in either OS and PFS between young and elderly patients. Although dose-adjusted EPOCH was associated with a high incidence of neutropenia, this was not accompanied by a large number of febrile neutropenia episodes, and there were no treatment-related deaths. This might be due to the short duration of neutropenia and the dose-adjustment paradigm introduced to reduce the dose if severe hematologic toxicity occurred.

This study has several limitations. It included a relatively small number of patients and the median follow-up time was short. In addition, in this study, the biology of PTCL, including molecular subtypes within PTCL diagnoses, was not evaluated. Although we cannot avoid any selection bias beyond PIT, stage, and age, etc. The 2-year PFS and OS were encouraging, and more robust data with longer-term follow up in the form of randomized controlled trials are needed to confirm the excellent response rates and survival with dose-adjusted EPOCH therapy. Recently, a number of novel agents, including histone deacetylase inhibitors, antifolates, immunomodulatory agents, nucleoside analogs, and other targeted agents, have been developed. Some of these novel agents can be combined with dose-adjusted EPOCH therapy and their relevant combination therapies should be identified.

In conclusion, our results indicate that dose-adjusted EPOCH had a high response rate and may improve outcomes for PTCL patients. This regimen has an acceptable toxicity profile, even in elderly patients with poor prognoses in whom approaches such as transplantation may not be feasible. Dose-adjusted EPOCH may be considered as a first-line approach for PTCL.

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