CHOEP-21 Chemotherapy for Newly Diagnosed Nodal Peripheral T-Cell Lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital

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Objective: *To determine the effectiveness and tolerability of the combination of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) with the addition of etoposide (CHOEP-21) for newly diagnosed nodal peripheral T-cell lymphomas (PTCLs).*

Material and Method: *Between January 2009 and October 2011, patients aged 18 to 60 years with newly diagnosed nodal PTCLs at the Maharaj Nakorn Chiang Mai Hospital were enrolled to receive CHOEP-21 every three weeks for eight cycles. G-CSF prophylaxis was given to all patients.*

Results: *Twenty-four patients were enrolled. Twenty of them were male with a median age of 49 years. The majority of patients (66.7%) had PTCL, not otherwise specified (PTCL, NOS), and 95.8% of the patients were in stage III or IV. The overall response rate was 58% with 42% having complete response. The response rates were better among patients with ALK-negative anaplastic large cell lymphoma (ALCL; 100%) and angioimmunoblastic T-cell lymphoma (AITL; 85%) than those with PTCL, NOS (44%). With a median follow-up of 21 months, the patients had an estimated 2-year event-free survival, and an overall survival rate of 37.6% and 54.4%, respectively. The most common adverse effects were infection and hematologic toxicities that was manageable.*

Conclusion: *Although CHOEP-21 induced favorable responses in patients with ALK-negative ALCL and AITL, the responses were not durable and further therapy is mandated in management of patients with nodal PTCL.*

Keywords: *T-cell lymphomas, CHOEP-21 chemotherapy*

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T-cell non-Hodgkin lymphomas (T-NHLs) is an uncommon type of lymphomas[1] accounting for 10% of all lymphomas in Thailand[2]. The common subtypes include extranodal NK/T-cell lymphoma, nasal type and nodal peripheral T-cell lymphoma (PTCLs), which is composed of PTCL, not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL). The nodal PTCLs, except ALCL, ALK-positive, have a poor prognosis in comparison with the aggressive B-cell lymphomas[3] with a 5-year overall survival rate (OS) of about 27%[4].

There is no standard treatment for nodal PTCLs. Intensive chemotherapy regimens for nodal PTCLs do not improve overall survival in comparison with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy[5] or other anthracycline-based chemotherapy regimens[6].

Several etoposide-containing chemotherapy regimens have demonstrated survival benefit for patients with PTCLs[7-10]. In the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL), the addition of etoposide in CHOP regimen (CHOEP-21) for the treatment of a good prognosis aggressive NHL, showed an improvement with a complete response (CR) rate and event free survival (EFS) rate for patients aged less than 60 years old[9]. Large cohort from German including that in this present study showed that etoposide improved 3-year EFS in the subgroup of T-NHL patients (75.4% versus 51%)[10].

In the present study, we report the efficacy and side effects of CHOEP-21 in the treatment of

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newly diagnosed nodal PTCLs in the Maharaj Nakorn Chiang Mai Hospital in Thailand.

Material and Method

This prospective case series of study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chiang Mai University, Thailand and performed at the Maharaj Nakorn Chiang Mai Hospital. Written informed consent was obtained according to the Declaration of Helsinki. Between January 2009 and October 2011, patients with diagnosis of nodal PTCLs were enrolled in the trial. Eligibility criteria included (1) previously untreated nodal PTCLs including PTCL-NOS, AITL, or ALCL, ALK-negative, (2) confirmation of the histopathologic diagnosis by hematopathologist, and (3) ages greater than 18 years and less than 60 years. The exclusion criteria included (1) HIV infection, (2) major organ dysfunction except those related to lymphoma such as ejection fraction of less than 40%, significant abnormal liver function test defined as AST, ALT or serum alkaline phosphatase of more than three times the upper normal limit or serum bilirubin levels higher than 2.5 mg/dl, creatinine clearance of less than 30 ml/min, (3) Eastern Cooperative Oncology Group (ECOG) performance score of 4, (4) pregnancy or lactation, (5) patients with active infection, and (6) patients with hypersensitivity to etoposide.

Staging

Patients were clinically staged according to the Ann Arbor classification. Initial investigations included a complete medical history and physical examination, complete blood count (CBC), blood urea nitrogen (BUN), creatinine, electrolyte, lactate dehydrogenase (LDH), uric acid, liver function test, HBsAg, anti-HCV, anti-HIV, pregnancy test in sexually active women, stool concentration for parasite, bone marrow biopsy, chest x-Ray (CXR), computed tomography of the chest and abdomen, electrocardiogram (EKG) and echocardiogram in patients clinically suspected of heart disease.

Treatment schedule

The patients were given CHOEP-21 regimen (Cyclophosphamide 750 mg/m^2 intravenously on day 1, Doxorubicin 50 mg/m^2 intravenously on day 1, Vincristine 1.4 mg/m^2 intravenously on day 1, Prednisolone 100 mg orally on day 1-5 and Etoposide 100 mg/m^2 intravenously on day 1-3). All patients received recombinant human granulocyte colony-stimulating factor (G-CSF; filgastrim) 300 microgram/day from day 4 to 11. The regimen was repeated every three weeks for eight cycles. If the blood counts did not recover and the chemotherapy was delayed for one week, the dosages of myelosuppressive agents were reduced by 25%, or by 50% if the delay was more than two weeks. Involved field irradiation was given in bulky disease (a tumor size of greater than 10 centimeters or mediastinal nodes size larger than one-third of the thorax at the thoracic spine level 6).

Anti-infective prophylaxis

Acyclovir 400 mg was given twice a day for prophylaxis against herpes virus infection. Sulfamethoxazole-trimethoprim 800/160 mg was given twice a week against *Pneumocystis jiroveci*. Fluconazole 200 mg/day against fungal infection were also given. For chronic hepatitis B carriers, lamivudine 150 mg/day was given to prevent hepatitis B virus reactivation.

Disease evaluation

The hematologic, biochemical, and radiologic tests were repeated after the fourth course of chemotherapy and at the end of the therapy. Bone marrow biopsy was repeated if there were signs of bone marrow invasion at diagnosis. After the completion of eight cycles, the patients were followed-up every three months in the first two years and then every six months thereafter. The response assessment was made according to The International Working Group (IWG) response criteria[11].

For patients having either hematologic or non-hematologic adverse events of more than grade 2, the chemotherapy was held off for one to three weeks until the side effects were less than that of grade 2 according to the Common Toxicity Criteria for Adverse Events (CTCAE version 3).

Patients having stable disease or progressive disease after four cycles of chemotherapy or having a grade 3 toxicity or greater for more than four weeks, were subsequently withdrawn from the study protocol.

Statistical analysis

The primary endpoint of the study was EFS, calculated from the date of diagnosis until disease progression, or relapsed, a change to other treatment, or death from any cause. The secondary endpoint of

the study was OS, response rate and toxicities of the regimen. OS was calculated from the date of diagnosis until death from any cause. EFS and OS curves were calculated according to the Kaplan-Meier method. The response rate was calculated from the ratio of CR and PR by descriptive analysis and the factors influencing the response rate were analyzed by the univariate and multivariate logistic regression model. The side effects were analyzed according to descriptive analysis. EFS, OS, response rate were compared with historical control patients with nodal PTCLs, except ALK-positive ALCL, who received CHOP-21 regimen in the Maharaj Nakorn Chiang Mai Hospital during the year 1998-2008 as additional analysis. The patients characteristics were compared between the 2 treatment arms using the Fisher's exact test or the Pearson Chi-square test in cases of discrete variables, or the Wilcoxon rank sum test in cases of continuous variables. The response end points were compared between the two treatment arms using logistic regression and EFS and OS were compared according to the Kaplan-Meier method. All data were analyzed using the SPSS version 16.0.

Results

Clinical characteristics of the patients

The clinical characteristics of the 24 patients are listed in Table 1. The median age was 49 years. Almost all except for one were in stage III-IV, 72% had IPI at least 2. No patient presented with bulky disease. Bone marrow involvement was found in six patients and one patient presented with hemophagocytic syndrome.

Treatment feasibility and dose intensity

The relative dose intensity (RDI) was calculated. The mean dose intensity was 226.1 mg/m^2/week (RDI 90.4%) for cyclophosphamide, 14.8 mg/m^2/week (RDI 88.9%) for doxorubicin, 0.38 mg/m^2/week (RDI 80.3%) for vincristine, 18.8 mg/m^2/week (RDI 93.9%) for prednisolone, and 89.7 mg/m^2/week for etoposide (RDI 89.7%).

Treatment response

The response is summarized in Table 2. Among the 24 patients, 10 (42%) reached CR, and four (16%) had PR, with an overall response rate (CR and

Table 1. Comparison between CHOEP and CHOP historical control patient characteristics and outcome

Parameter	CHOEP-21	CHOP-21	p-value
Number of patients	24	11	-
Age, mean ± SD y (range)	48.9±9.9 (18-60)	48.4±10.3 (25-60)	0.683
Sex (male:female ratio)	20:4	5:6	0.041
Histologic subtype, No. patients (%)			
PTCL, NOS	16 (64)	7 (64)	1.000
Non-PTCL, NOS (ALCL, ALK-negative: AITL)	8 (1:7; 36%)	4 (0:4; 36%)	
Ann Arbor stage IV, No. patients (%)	15 (63)	4 (36)	0.273
B symptoms, No. patients (%)	12 (50)	4 (36)	0.257
Bone marrow involvement, No. patients (%)	6 (25)	1 (9)	0.392
Elevated LDH serum level, No. patients (%)	14 (58)	7 (64)	1.000
Bulky disease (%)	0 (0)	0 (0)	-
IPI score at least 2, No. patients (%)	15 (72)	5 (46)	0.467
0-1	9 (38)	6 (54)	
2-3	12 (50)	3 (27)	
4-5	3 (12)	2 (18)	
CR (%)	10 (42)	8 (72)	0.146
Overall response rate; CR + PR (%)	14 (58)	8 (72)	0.709
Relapse/refractory (%)	12 (50)	5 (45)	1.000

CHOEP = cyclophosphamide, doxorubicin, vincristine etoposide and prednisolone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; PTCL, NOS = peripheral T-cell lymphoma, not otherwise specified; ALK-negative ALCL = anaplastic lymphoma kinase-negative large cell lymphoma; AITL = angioimmunoblastic T-cell lymphoma; LDH = lactate dehydrogenase; IPI = international prognostic index; CR = complte response; PR = partial response

Table 2. Response to treatment of 24 patients with nodal PTCLs according to histopathology

Histopathology	Total	CR (%)	PR (%)	PD (%)	Relapsed (%)	Alive in remission (%)	Alive (%)
PTCL, NOS	16	4 (25)	3 (19)	9 (56)	3 (19)	3 (19)	8 (50)
AITL	7	5 (71)	1 (14)	1 (14)	2 (29)	4 (57)	5 (71)
ALCL, ALK-negative	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)
Total	24	10 (42)	4 (16)	10 (42)	5/14 (36)	8 (33)	14 (58)

PD = progression of disease

Table 3. Univariated analysis for factors to response (CR and PR)

Factors	p-value
Age less than 40 years versus more than 40 years	1.000
AITL and ALCL, ALK-negative versus PTCL, NOS	0.178
Stage II or III versus IV	0.080
No versus presence of bone marrow involvement	0.001
IPI 0-1 versus 2-5	0.080
LDH more than upper normal limit	0.210

PR) of 58%. One ALK negative-ALCL (100%) and five out of seven cases of AITL (71%) entered CR, while only four of the 16 PTCL-NOS patients (25%) achieved CR. In the univariate analysis, only bone marrow involvement correlated with the probability of response in the present study (Table 3).

Seven patients who had progression of the disease (PD) during CHOEP-21 received salvage chemotherapy but almost all except for one were refractory to the treatment. The other three patients did not receive further treatment due to infection and poor performance status.

After a median follow-up of 21 months, eight (57%) of the 14 patients with initial response could maintain their remission status, but five patients (36%) relapsed and one (7%) patient died from pulmonary tuberculosis. Four of the relapsed patients received salvage chemotherapy with good response.

Comparison with historical controls

The baseline characteristics and outcomes of 11 patients receiving CHOP are shown in Table 1. When compared with patients in the present study, the baseline characteristics were not statistically different except for the significant predominance of female in CHOP regimen group.

The overall response rate (58% and 72%) and CR rate (42% and 72%) were not significantly different between CHOEP and CHOP regimen. As shown in Fig. 1 and 2, the EFS and OS curve are projected to 37.6% and 54.4% at 2-year, respectively in CHOEP regimen compared with EFS of 51.4% and OS of 51.9% in CHOP regimen (p = 0.40 and p = 0.65 respectively).

Adverse events

Toxicity was evaluated for all 24 patients who were treated with CHOEP-21 in the 146 courses.

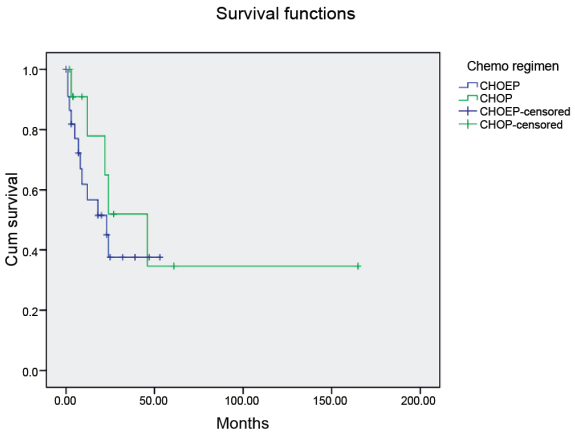

Fig. 1 Kaplan Meier curve for EFS in CHOEP and CHOP regimen.

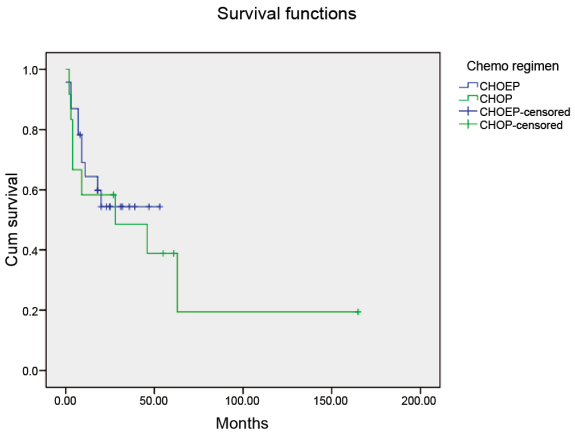

Fig. 2 Kaplan Meier curve for OS in CHOEP and CHOP regimen.

Hematologic toxicity

Neutropenia was by far the most frequent toxicity, with grade 3 or 4 occurring in 13 cycles (8.9%) and grade 1 or 2 in 19 (13%) cycles of chemotherapy. Thrombocytopenia occurred less frequently, with grade 3 or 4 in five (3.4%) cycles and grade 1 or 2 in only two (1.4%) cycles. Anemia was quite frequent, with a reduction of hemoglobin levels of more than 2 g/dL from the baseline values in six (25%) patients at the end of treatment.

Non-hematologic toxicity

Infection was common with grade 3 or 4 in 10 (6.8%) cycles of chemotherapy, in which febrile neutropenia developed in seven (4.8%) cycles. Other serious grade 3 or 4 infection, which each occurred once (0.7%) of chemotherapy cycle, included pulmonary tuberculosis, nocardiasis, sinusitis, urinary tract infection, and acute gastroenteritis. Grade 1 or 2 infection occurred in eight (5.5%) of 146 cycles (2 diarrhea, 1 cellulitis of the left toe, 1 skin abscess, 1 sinusitis, 1 Strongyloides infestation, and 1 Giardia infestation). Grade 3 cardiotoxicity was reported in one patient with underlying valvular heart disease. One patient developed hepatotoxicity grade 2, which was reversible after withholding fluconazole. Vomiting grade 1 was reported in only four cycles (2.7%). No neurotoxicity occurred during this study.

Discussion

The treatment outcomes of nodal PTCLs except ALK-positive ALCL is still poor in comparison with aggressive B-cell NHL as the result recommendation for treatment is either enrolling the patient in clinical trials or performing autologous hematopoietic stem cell transplantation (ASCT) in the first CR[12-15]. A minority of patients in Thailand can afford ASCT, so the physicians usually resort to the highly effective chemotherapy regimens for the management of nodal PTCLs in our country. Among several chemotherapy regimens that have been used for treating nodal PTCL patients, CHOEP-21 and cyclOBEAP regimens[16] were found to have beneficial impacts on the outcome. In comparison, CHOEP-21 regimen achieved better complete remission and 5-year event-free survival rate than CHOP[9,10], CHOEP is a very practical chemotherapy regimen in terms of drug administration compared to other regimens, availability of the drugs and its reasonable price. Although the patients treated with cyclOBEAP regimen could achieve a very high CR rate of 92% and a 5-year progression free survival rate (PFS) of 69%, its drawback was a very high frequency of grade 4 neutropenia (90%)[16].

We have learned from DSHNHL study that CHOEP-21 was well tolerated in patients aged less than 60 years but neutropenia was the most important side effect. Therefore, in the present study, G-CSF support and anti-infective prophylaxis were included. In addition, CHOEP-21 had no benefit and caused significant neutropenia in the elderly compared to CHOP-21 regimen, so patients older than 60 years were not included[17].

In the present study, the overall response rate of 58% with a CR rate of 42% and a 2-year EFS of 37.6% were inferior to other etoposide-based regimens that had been previously reported[7-10,16,18]. Many factors determined the difference in the outcome of the present study, for example, patient characteristics, histopathological subtype, stage of diseases and chemotherapy regimens received. Furthermore, serum LDH levels of the patients enrolled were normal in DSHNHL study[9], but were elevated in more than half of the patients in the present study.

Difference in histopathology could result in different degrees of clinical outcome. For example, the study of dose-adjusted (DA)-EPOCH regimen revealed that the outcomes of ALK-positive ALCL improved but was still disappointing for other histology[18]. The analysis among the different histological subtype of PTCL revealed that ALK-positive ALCL got significant benefit from CHOEP-21 in DSHNHL study, while eight patients with Ki-1 positive ALCL out of 27 PTCLs had high CR rate of 88% in which the whole group had CR rate of 77% in VACPE study[8]. In the present study, the majority of histological subtype was PTCL, NOS, especially ALK-positive ALCL patients were excluded from the present study contributing to a poorer outcome.

When comparing historically to CHOP-21 regimen, CHOEP-21 regimen seems to have a lower CR and an overall response rate but no statistically significant differences. This may be because of the low number of patients included in the present study, and the patients who received CHOP-21 regimen tended to have lower stage and lower IPI than who received CHOEP-21 regimen.

The important side effect of CHOEP-21 regimen is hematologic toxicity, especially neutropenia that can cause serious infections. In the present study, even with G-CSF support and anti-infective agents prophylaxis, some patients still suffered from these

adverse events, with grade 3 or 4 neutropenia in 8.9% and infection grade 3 or 4 in 6.8%, but the occurrence rate was less than those in previous reports[9]. However, most of patients tolerated this regimen well.

Some disadvantages of the present study included a small sample size, not being a randomized controlled trial and a short follow-up period.

Conclusion

The treatment outcome of PTCLs with existing chemotherapy regimen is not satisfactory. The results of the treatment can vary depending on several factors. Novel agents should be considered for improving the clinical outcome of these patients.

What is already known on this topic?

There is no standard treatment for nodal PTCLs. The current treatment includes multiagent chemotherapy such as CHOP regimen with or without autologous stem cell transplantation (ASCT) in high-risk patients. The addition to etoposide in CHOP regimen (CHOEP-21) showed an improvement of event free survival (EFS) rate in a German study[10] and this regimen is an option for the treatment according to NCCN guideline[12].

What this study adds?

This prospective study showed that CHOEP-21 did not seem to improve outcomes in patients with nodal PTCLs. However, CHOEP-21 induced favorable responses in patients with ALK-negative ALCL and AITL compare to PTCL, NOS. These findings supported the recommendation to enroll nodal PTCLs patients in clinical trials or consider ASCT after induction chemotherapy.

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Potential conflict of interest

None.

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ยาเคมีบำบัดสูตร CHOEP-21 สำหรับผู้ป่วย nodal peripheral T-cell lymphoma รายใหม่ในโรงพยาบาลมหาราชนครเชียงใหม่

เอกรัฐ รัฐฤทธิ์ธำรง, ลลิตา นรเศรษฐ์ธาดา, อดิศักดิ์ ตันติวรวิทย์, ชาตรี ชัยอดิศักดิ์โสภา, วีระศักดิ์ นาวารวงศ์

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพและการทนต่อยาเคมีบำบัดสูตร cyclophosphamide, doxorubicin, vincristine และ prednisolone (CHOP) ร่วมกับ etoposide (CHOEP-21) สำหรับผู้ป่วย nodal peripheral T-cell lymphoma (PTCL) รายใหม่*

วัสดุและวิธีการ: *รวบรวมผู้ป่วยซึ่งได้รับการวินิจฉัยเป็น nodal PTCL รายใหม่อายุ 18-60 ปี ที่โรงพยาบาลมหาราชนครเชียงใหม่ ตั้งแต่เดือนมกราคม พ.ศ. 2552 ถึง เดือนตุลาคม พ.ศ. 2554 เข้ารับการรักษาโดยยาเคมีบำบัดสูตร CHOEP-21 ทุก 3 สัปดาห์ จำนวน 8 รอบ ร่วมกับการให้ G-CSF ป้องกันเม็ดเลือดขาวต่ำในผู้ป่วยทุกราย*

ผลการศึกษา: *มีผู้ป่วย 24 ราย เข้าร่วมการศึกษา ผู้ป่วย 20 ราย เป็นเพศชาย อายุเฉลี่ย 49 ปี ผู้ป่วยส่วนใหญ่ (ร้อยละ 66.7) เป็น PTCL, not otherwise specified (PTCL, NOS) ผู้ป่วยร้อยละ 95.8 อยู่ในระยะที่ 3 และ 4 อัตราการตอบสนองโดยรวม ร้อยละ 58 เป็น complete response ร้อยละ 42 การตอบสนองจะดีมากในผู้ป่วย ALK-negative anaplastic large cell lymphoma (ALCL; ร้อยละ 100) และในผู้ป่วย angioimmunoblastic large cell lymphoma (AITL; ร้อยละ 85) ต่างจากในผู้ป่วย PTCL, NOS (ร้อยละ 44) จากการติดตามเฉลี่ย 21 เดือน event-free survival และ overall survival ที่ 2 ปี เท่ากับ ร้อยละ 37.6 และร้อยละ 54.4 ตามลำดับ ผลข้างเคียงที่พบบ่อยคือ การติดเชื้อ และผลข้างเคียงทางระบบโลหิตวิทยา*

สรุป: *ยาเคมีบำบัดสูตร CHOEP-21 ให้อัตราการตอบสนองที่ดีมากในผู้ป่วย ALK-negative ALCL และ AITL แต่การตอบสนองสั้น จึงมีความจำเป็นในการให้การรักษาผู้ป่วยที่มี nodal PTCL ด้วยการรักษาอื่นต่อไป*
