Original Article

Prognostic Impact of p53, Bcl-2, and p-glycoprotein Expressions in Peripheral T-cell Lymphoma, Not Otherwise Specified (PTCL, NOS) in Thai Patients

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Abstract

Objective: *To define the expression of p53, Bcl-2, and p-glycoprotein and to correlate the findings with disease parameters, response to therapy, and clinical outcomes of patients with PTCL, NOS.* ***Materials and Methods:*** *Adult patients with diagnosis of PTCL, NOS were reviewed from 2001 to 2012. Clinical parameters and treatment outcomes data were extracted. The specimens were stained for p53, Bcl-2, and p-glycoprotein. The results were analyzed for association with disease stage, IPI, PIT score, response rate (RR), and overall survival (OS).* ***Results:*** *Forty-nine patients (38 males, 11 females) were enrolled. The median age was 58 years old. Of those, B symptoms were presented in 55% and elevated LDH in 54%. Eighty-two percent had good ECOG scores, 61% in stages III-IV, 80% with extranodal lesions, and 40% with marrow involvement. Sixty-three percent were classified as low to low-intermediate risk according to IPI and 46% had PIT score of 0-1. Most patients (74%) were treated by CHOP chemotherapy. Of 35 patients evaluated, the ORR overall response rate was 63% with 40% complete remission. P53, Bcl-2, and p-glycoprotein were positive in 84%, 47%, and 29%, respectively. Expression of these biomarkers was not significantly correlated with survivals nor any prognostic factors. Median survival was 16.2 months. With univariate analysis, OS was significantly associated with clinical stage, IPI, and PIT score but not with the biomarker expressions. All of them remained significance with multivariate analysis.* ***Conclusions:*** *PTCL, NOS presented more in males with extranodal lesions and advanced stage. Less than half of patients achieved CR with CHOP regimen. The expressions of p53, Bcl-2, and p-glycoprotein did not show any significant influence on prognostic predictors and OS.*

Keywords : ● *P53* ● *Bcl-2* ● *P-glycoprotein* ● *Peripheral T-cell lymphoma, not otherwise specified* ● *Survival*

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Introduction

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) is a heterogeneous category of nodal and extranodal mature T-cell lymphomas. This lymphoid neoplasmis the most common subtype of mature NK/T-cell lymphoma and classified according to the World Health Organization (WHO) classification of the hematopoietic and lymphoid neoplasms 2008.[1,2] Diagnosis is made when other specific entities derived from mature T lymphocytes have been excluded. Most of patients present with peripheral lymph node involvement and partly with generalized disease such

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as bone marrow (BM), liver, spleen, and extranodal tissues.[3] PTCL, NOS is more predominant in elderly male with advanced stage and high prognostic scores.[2]

PTCL, NOS accounts for 25.9% of all mature NK/T-cell lymphoma from the recent report by the International T-cell lymphoma project which more prevalent in North America and Europe.[2] The incidence in Thailand reported by the Thai Lymphoma Study Group was 31% of all PTCL.[4] Nowadays, there are various modalities of treatment but they produce unsatisfactory outcomes. The standard treatment in PTCL, NOS remains uncertain.

There are several investigators studied the apoptotic pathways and found their involvement in pathogenesis of lymphoid neoplasms including PTCL.[5-8] The expression of p53 and Bcl-2 have been shown to be significantly associated with PTCL progression and clinical outcomes.[9-10] In addition, p-glycoprotein which is involved in the resistance to several cytotoxic agents was also demonstrated in PTCL.[9,11] The purpose of this study was to define the expression of p53, Bcl-2, and p-glycoprotein and to correlate the findings with the disease parameters, response to therapy, and survival of Thai patients with PTCL, NOS.

Materials and Methods

The patients were enrolled from January 2001 to December 2012 at Songklanagarind Hospital. The eligibility criteria were patients who were 18 years oldor older and newly diagnosed as PTCL, NOS according to WHO classification 2008.[1] The diagnosis of PTCL, NOS was based on the histologic features which are described in WHO classification 2008.[1] Immunohistochemical staining had been performed using antibodies against T-, B-, and NK-cell differentiation antigens including CD3, CD4, CD5, CD8, CD20, CD30, CD56, CD79a, and TIA-1. In case of inconclusive diagnosis, T-cell receptor (TCR) gamma gene was performed for confirmation of monoclonality of the disease. The corresponding paraffin-embedded specimens were stained immunohistochemically for p53, Bcl-2, and p-glycoprotein.

The clinical parameters and treatment outcomes wereretrospectively reviewed from medical records. Extracted data included age, sex, clinical presentation, B symptoms, performance status (PS), clinical stage, lactate dehydrogenase (LDH) level, prognostic scores, treatment options, response, salvage therapy, and death. Clinical stage in this study was assessed by using Ann Arbor staging system. International Prognostic Index (IPI) including Ann Arbor stage, extranodal involvement, age, LDH level, and PS was also used.[12,13] Regarding IPI, the patients were classified into two groups: low to low-intermediate IPI and high-intermediate to high IPI. Moreover, this study also applied the Prognostic Index for PTCL, NOS (PIT score) based on age, PS, LDH level, and bone marrow involvement. According to PIT scoring system, the patients were subdivided into two groups: score 0-1 and score 2-4.[14]

This study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (EC: 55-113-14-3-3). All deaths were registered by the Department of Provincial Administration, Ministry of Interior, using certificates issued by a physician stating the cause of death. All living patients were confirmed directly by phone calling, mailing or checking the census records from the Hat Yai City Municipality.

Forty-nine patients were fulfilled the eligibility criteria and were recruited in this study.

Immunohistochemical study

Tumor samples were obtained by tissue biopsy at the time of the initial diagnosis. Immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue samples. The 5-μm-thick sections were cut on aminopropyltriethoxysilane-coated slides. The sections were stained for monoclonal antibodies of p53 (DO-7, DAKO, Glostrup, Denmark, 1:300), Bcl-2 (Novocastra Laboratories, UK, 1:450) and p-glycoprotein (Novocastra Laboratories, UK, 1:50) by using the automated BOND-

MAX system (Leica Biosystems).

Scoring was analyzed in the area of highest protein expression. The results were semiquantitatively scored as follows; score of 0 positivity when completely negative reactions were found inside the tumor cells and positive scores of 1+, 2+, 3+, and 4+ when < 10%, 10-50%, 51-90%, and > 90% of the tumor exhibited positive reactions, respectively. The cases exhibiting a majority of positive tumor cells (> 10% or ≥ 2+ positivity) were considered as positive expression. The tumor cells were differentiated from normal reactive T-cell lymphocytes by using morphology criteria and compared with hematoxylin and eosin (H&E) staining. The H&E and immunohistochemical staining results are shown in Figure 1.

Statistical analysis

Statistical analysis was done using Stata Software Packages, version 13.1. The clinical parameters and treatment outcomes were compared among patients with or without expressions of p53, Bcl-2, p-glycoprotein or combined Bcl-2/p53 using a Chi-square test. Survival analysis was performed with the Kaplan-Meier method. Overall survival (OS) was calculated as the time interval from the date of diagnosis to death or last follow-up. Survival analyses between subgroups were compared using log-rank test. Multivariate analyses for OS were performed using a Cox regression model. A cut-off *P* value of 0.05 was considered statistically significant for all statistical analyses.

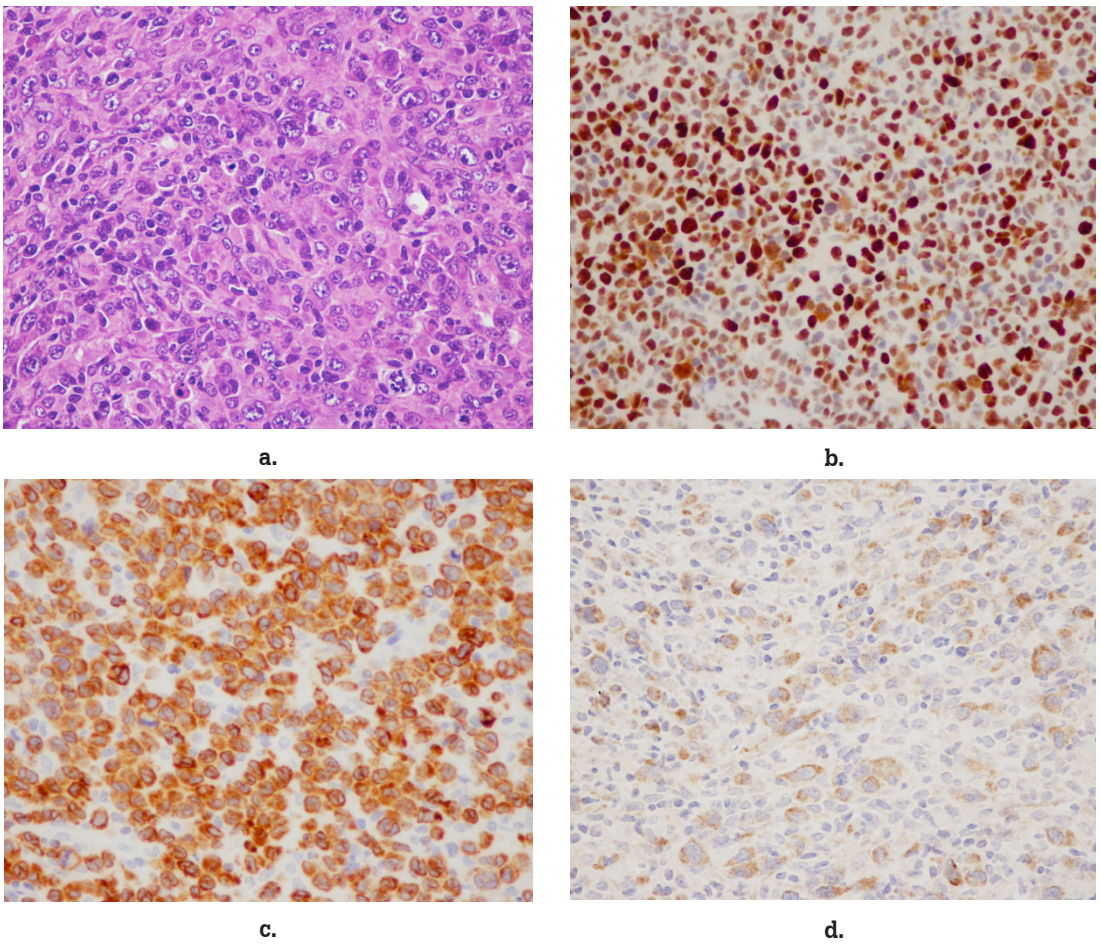

Figure 1. Immunohistochemical detection showing (x400), **a.** H&E staining in PTCL, NOS; **b.** strongly positive nuclear staining for p53 (4+); **c.** strongly positive cytoplasmic staining for Bcl-2 (4+); **d.** strongly positive cytoplasmic staining for p-glycoprotein (3+)

Results

Patient characteristics and treatment outcomes

Forty-nine patients were analysed in this study. They were 38 males and 11 females, giving male to female ratio of 3.5:1. The median age was 58 years old (range 18-89). B symptoms were presented in 55% and elevated LDH in 54% of the patients. Eighty-two percent had good ECOG scores, 61% in stages III-IV, 80% with extranodal lesions, and 40% with bone marrow involvement. Hemophagocytic activity was found in 10.5% of those who had marrow involvement. Sixty-three percent were classified as low to low-intermediate IPI and 46% had PIT score of 0-1. Most patients (74%) were treated by CHOP chemotherapy and only 10% by radiotherapy. Of the 35 patients evaluated, the overall response rate was 63% with 40% complete remission. The patient characteristics and treatment outcomes are summarized in Table 1.

The expression of p53, Bcl-2 and p-glycoprotein

The p53, Bcl-2, and p-glycoprotein positivity were demonstrated in 41 (84%), 23 (47%), and 14 (29%) patients, respectively. The expression of p53, Bcl-2, and p-glycoprotein were not significantly correlated with advanced stage, higher IPI, higher PIT score, and response rate. We also analyzed combined Bcl-2/p53 according to their expressions with clinical stage, IPI, PIT score, response rate, and survivals. The results did not show any significant association, as well.

Survival analysis

With median follow-up time of 15 months, the median survival was 16.2 months (Figure 2). There were 36 patients (73%) died in this study. Projected 3-year OS and 5-year OS were about 25% and 20%, respectively. Regarding the univariate analysis, OS was significantly associated with clinical stage ($p = 0.003$), IPI ($p = 0.000$), and PIT score ($p = 0.000$). On the contrary, the expression of p53, Bcl-2, p-glycoprotein or combined Bcl-2/p53 did not show prognostic significance on survival (Figure 3). Clinical stage ($p = 0.005$), IPI ($p = 0.000$) and PIT score ($p = 0.000$) all remained significance with multivariate analysis.

Table 1. Patient characteristics and treatment outcomes of 49 patients with PTCL, NOS

Variables	Number of patients (%)
Sex, M:F ratio	3.5:1
Median age (range), years	58 (18-89)
< 60	28 (57)
≥ 60	21 (43)
Performance status, ECOG	
0-1	40 (82)
2-4	9 (18)
Stage	
I-II	19 (39)
III-IV	30 (61)
LDH > normal	26 (54)
Extranodal involvement	39 (80)
B symptom	27 (55)
Bone marrow involvement	19 (40)
IPI	
Low to Low-intermediate	30 (63)
High-intermediate to High	18 (37)
PIT	
Score 0-1	22 (46)
Score 2-4	26 (54)
Initial treatment	
None	7 (14)
Chemotherapy	
CHOP	36 (74)
Others	6 (12)
Radiation therapy	5 (10)
Response	
ORR	22 (63)
CR	14 (40)
PR	8 (23)
SD	0 (0)
PD	13 (37)
Salvage therapy	19 (39)
Death	36 (73)

ECOG = Eastern Cooperative Oncology Group; *LDH* = Lactate dehydrogenase; *IPI* = International Prognostic Index; *PIT* = Prognostic index for PTCL; *CHOP* = cyclophosphamide/doxorubicin/vincristine/prednisolone; *ORR* = overall response rate; *CR* = complete remission; *PR* = partial response; *SD* = stable disease; *PD* = progressive disease

Discussion

PTCL, NOS is the most common subtype of mature NK/T-cell lymphoma.[1,2] This entity is also common in Thailand as the report by the Thai Lymphoma Study Group.[4] Similar to other previous studies[9,10], our patients also showed male predominance (M:F ratio 3.5:1) with median age of 58 years, advanced stage in

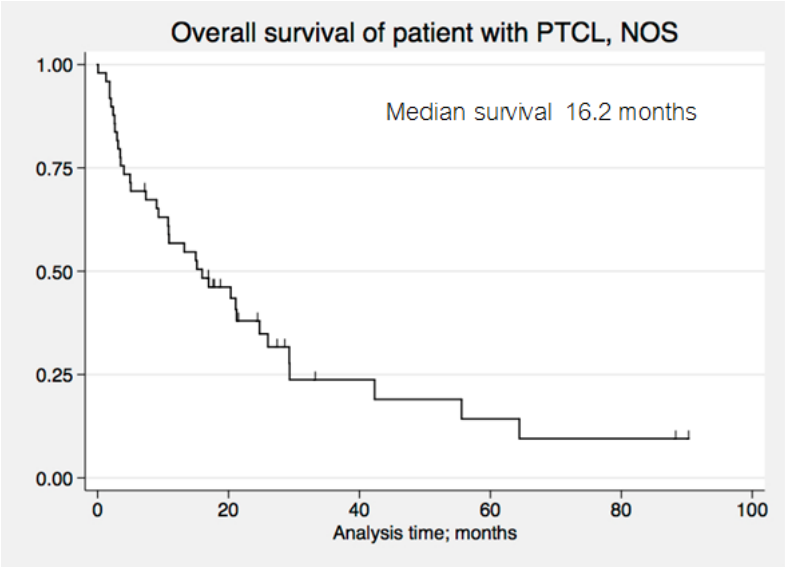

Figure 2. Overall survival of patients with PTCL, NOS

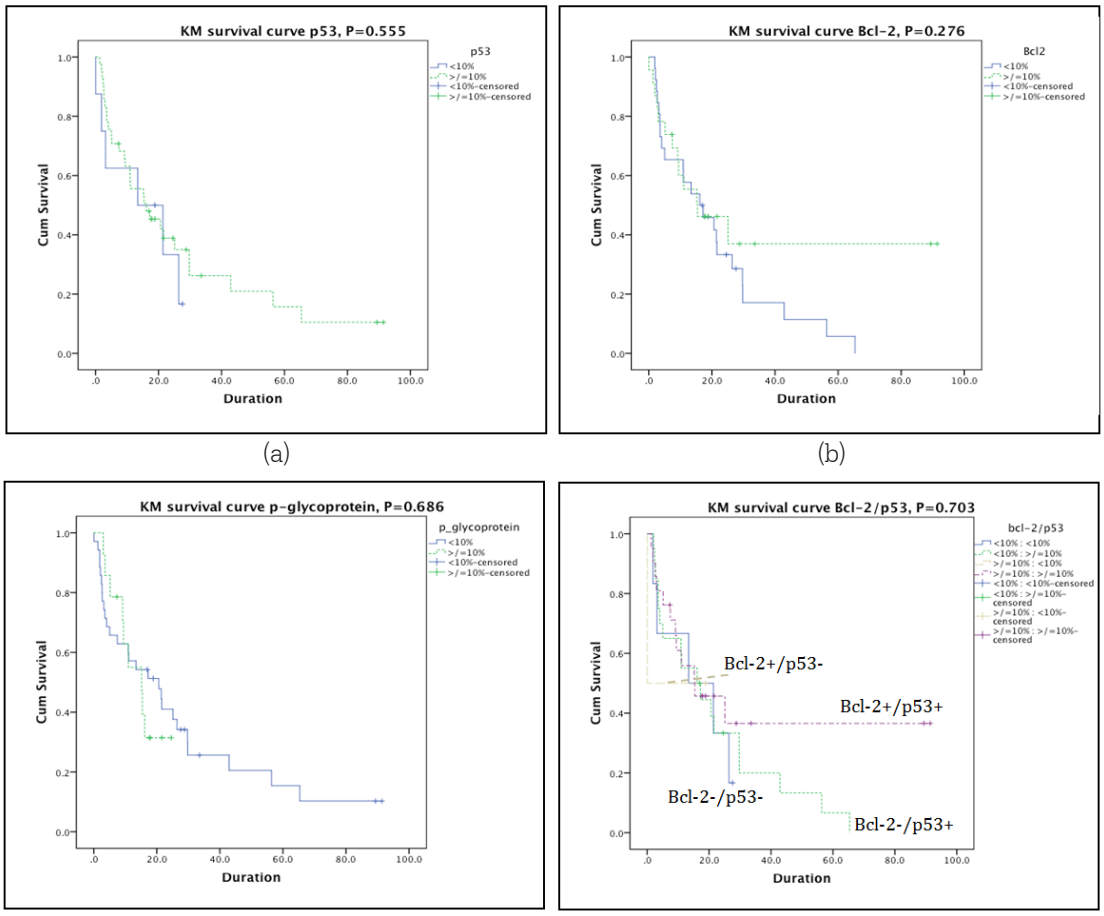

Figure 3. Effects of p53 (a), Bcl-2 (b), p-glycoprotein (c), and combined Bcl-2/p53 (d) on overall survival of patients with PTCL, NOS

61%, high frequency of extranodal involvement in 80% and high PIT score in 54%. Without standard treatment for PTCL, NOS. The treatment of patients would be a clinical trial as the best initial treatment option.[15] According to the International T-cell Lymphoma Project, the survival of PTCL, NOS, was poor with a 5-year OS and failure free survival were 32% and 20%, respectively.[2] Therefore, the biological factors are needed to investigate and identify the patients who might be beneficial from intensive therapeutic approaches.

The expression of p53 and Bcl-2 have been shown to be significantly associated with PTCL progression and clinical outcomes.[9-10] P53 is a nuclear phosphoprotein encoded by a tumor suppressor gene located on chromosome 17p13. P53 plays a major role in cell cycle control, DNA repair, and apoptosis. Loss of p53 function may cause resistance to apoptosis.[16] Pescamona et al reported that p53 expression is significantly associated with poorer response to intensive chemotherapy in high-graded nodal PTCL.[6] The Bcl-2 also had been investigated, it proved to block programmed cell death in transgenic mice that overexpressed Bcl-2 in the B-cell lineage with extended cell survival and progressed to high-grade lymphoma.[17] Rassidakis et al found that the Bcl-2 expression correlated with apoptosis and proliferation index of PTCL.[8] Moreover, the study by Jung et al also reported that Bcl-2 overexpression seemed to correlated with the progression of PTCL interacting with a p53-dependent pathway.[10]

P-glycoprotein is another biomarker in this study, functions as an energy-dependent drug efflux pump and causes a reduction in intracellular drug concentration. The resistance to several cytotoxic agents from p-glycoprotein were demonstrated in PTCL.[9-11]

In our study, p53 expression was detected in the majority of cases (84%) while Bcl-2 and p-glycoprotein expressed in 47% and 29%, respectively. Regarding treatment, CHOP chemotherapy is the main modality, but less than half of the patients achieved CR. The median survival was 16.2 months and projected 5-year OS was 20%. In the survival analysis, OS was significantly associated with clinical stage, IPI, and PIT score. The expression of p53, Bcl-2, p-glycoprotein or combined Bcl-2/p53 did not show prognostic significance on survival.

Compared to previous studies, the patient characteristics and treatment responses were comparable (Table 2). The expression of Bcl-2 and p-glycoprotein were in similar proportions. Although projected 3-year OS of patients with positive Bcl-2 was lower than those with negative Bcl-2 (38% vs 18%) [Figure 3(b)], this difference was not statistically significant ($p = 0.267$). The reason might be due to a small number of patients. On the contrary, the proportions of p53 expression were higher in this study (Table 2). The overall response rate in this study was high and comparable with other studies but CR rate is less and it produced unsatisfactory survival. We could not demonstrate the effect of p53 on OS while Pescamona et al found that p53 expressed in only 29% of patients with PTCL, NOS and it was significantly associated with OS and EFS. The explanation for these findings might be multifactorial as high p53 expression may give high proportion of death and unfavourable outcome, a low number of patients, ethnicity, environmental settings e.g. economic status, modalities of treatment, supportive care and heterogeneity of disease, as well. Further study with more number of patients will probably solve this problem.

Conclusions

PTCL, NOS presented more in males with extranodal lesions and advanced stage. Less than half of the patients achieved CR with CHOP regimen. P53, Bcl-2, p-glycoprotein or combined Bcl-2/p53 expression did not show any significant influence on

Table 2. Clinical comparison with previous studies

Variables	This study (n = 49)	Jung et al, 2006[10] (n = 74)	Pescarmona et al, 2001[9] (n = 45)
M:F ratio	3.5:1	2.2:1	2.2:1
Median age (years)	58	46	55
Histology subtypes (%)			
PTCL, NOS	100	60	100
LDH > normal (%)	54	38	56
IPI (%)			
L-LI	63	53	67
HI-H	37	47	33
PIT (%)			
Score 0-1	46	73	0
Score 2-4	54	27	0
Biomarkers expression (%)			
p53	84	45	28.9
Bcl-2	47	45	51.1
p-glycoprotein	29	0	17.8
Treatment (%)			
None	14	8	0
Chemotherapy	86	64	86
Radiation therapy	10	4	
Response (%)			
ORR	63	75	0
CR	40	64	64.1
PR	23	11	0
NR	37	0	37
Death (%)	73	32	37
Overall survival	Median 16.2 months	3-year OS 82.5%	
Conclusions	OS was associated with clinical stage, higher IPI and PIT score *(p < 0.00)*	Bcl-2 was associated with stage (*p = 0.021*), IPI (*p = 0.038*) Bcl-2/p53 was associated with advanced stage (*p = 0.008*) and higher IPI (*p = 0.001*)	P53 was significant in OS (*p = 0.0032*) and EFS (*p = 0.0004*) Bcl-2 was significant in EFS (*p = 0.0491*)

M = male; *F* = female; *LDH* = lactate dehydrogenase; *IPI* = International Prognostic Index; *L-LI* = low to low-intermediate; *HI-H* = high-intermediate to high; *PIT* = Prognostic index for PTCL; *ORR* = overall response rate; *CR* = complete remission; *PR* = partial response; *NR* = no-response; *OS* = overall survival; *EFS* = event free survival; *NA* = not available

clinical outcomes such as RR and OS. The number of patient in this study was small. Therefore, larger number of patients with other biomarker expressions are needed for further investigation.

Acknowledgement

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การแสดงออกของ p53, Bcl-2 และ p-glycoprotein และความสัมพันธ์กับการพยากรณ์โรคในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด PTCL, NOS

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บทคัดย่อ

วัตถุประสงค์ *เพื่อศึกษาอัตราการแสดงออกของ p53 Bcl-2 และ p-glycoprotein และความสัมพันธ์ระหว่างการแสดงออกของสารโปรตีนกับพยากรณ์โรคและอัตราการรอดชีวิตในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด PTCL, NOS* ***วัสดุและวิธีการ*** *ศึกษาย้อนหลังในกลุ่มผู้ป่วยผู้ใหญ่ที่ได้รับการวินิจฉัยโรคมะเร็งต่อมน้ำเหลืองชนิด PTCL, NOS ตั้งแต่ปี พ.ศ. 2544-2555 โดยเก็บข้อมูลพื้นฐานทางคลินิกและผลการรักษาของผู้ป่วย ร่วมกับศึกษาการแสดงออกของ p53 Bcl-2 และ p-glycoprotein ในชิ้นเนื้อที่ย้อมเพิ่มเติมด้วยวิธี immunohistochemistry นำผลการศึกษาทั้งหมดมาวิเคราะห์เพื่อหาความสัมพันธ์กับระยะโรค ปัจจัยการพยากรณ์โรค อัตราการตอบสนองต่อการรักษา และอัตราการรอดชีวิต* ***ผลการศึกษา*** *มีผู้ป่วยในการศึกษาทั้งหมด 49 ราย (หญิง 38 รายและชาย 11 ราย) ค่ามัธยฐานของอายุเท่ากับ 58 ปี ผู้ป่วยมี B symptom ร้อยละ 55 และมี LDH สูง ร้อยละ 54 ผู้ป่วยส่วนใหญ่อยู่ใน good ECOG score (ร้อยละ 82) และโรคอยู่ในระยะ III-IV (ร้อยละ 61) ร้อยละ 80 ของผู้ป่วยทั้งหมดมีอาการแสดงนอกต่อมน้ำเหลือง และร้อยละ 40 มีโรคในไขกระดูก เมื่อจำแนกตามปัจจัยการพยากรณ์โรคพบว่าผู้ป่วยร้อยละ 63 จัดอยู่ในกลุ่ม low-low-intermediate IPI และร้อยละ 46 มี PIT score 0-1 ผู้ป่วยร้อยละ 74 ได้รับการรักษาด้วยยาสูตร CHOP มีผู้ป่วยทั้งหมด 35 รายจากทั้งหมดที่ประเมินการตอบสนองพบว่าอัตราการตอบสนองต่อการรักษาคิดเป็นร้อยละ 63 และอัตราโรคสงบร้อยละ 40 อัตราการแสดงออกของ p53 Bcl-2 และ p-glycoprotein คิดเป็นร้อยละ 84 47 และ 29 ตามลำดับ การแสดงออกของสารโปรตีนดังกล่าวไม่สัมพันธ์กับการรอดชีวิตหรือการพยากรณ์โรคของผู้ป่วย ผู้ป่วยในการศึกษามีอัตราการรอดชีวิตเฉลี่ย 16.2 เดือน จากการวิเคราะห์ปัจจัยที่มีความสัมพันธ์กับอัตราการรอดชีวิต พบว่าระยะของโรค IPI และ PIT score มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติทั้งจากการวิเคราะห์แบบ univariate และ multivariate* ***สรุป*** *ผู้ป่วย PTCL, NOS ส่วนใหญ่เป็นเพศชาย มักจะมีอาการแสดงนอกต่อมน้ำเหลืองและมีการดำเนินโรคอยู่ในระยะรุนแรง การรักษาด้วยยาสูตร CHOP นั้นทำให้ผู้ป่วยเข้าสู่ระยะโรคสงบได้น้อยกว่าร้อยละ 50 การแสดงออกของ p53 Bcl-2 และ p-glycoprotein ไม่มีความสัมพันธ์กับปัจจัยพยากรณ์โรคและอัตราการรอดชีวิต*

คำสำคัญ : ● *P53* ● *Bcl-2* ● *P-glycoprotein* ● *Peripheral T-cell lymphoma, not otherwise specified* ● *Survival*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2557;24:119-27.