The Expressions of P53, Bcl-2, and P-Glycoprotein and Prognostic Impact in Patients with Peripheral T-Cell Lymphoma (PTCL)

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Objective: *To define the expressions of p53, Bcl-2, and p-glycoprotein and prognostic impact in patients with peripheral T-cell lymphoma (PTCL).*
Material and Method: *Adult patients with newly diagnosed as PTCL were reviewed from 2001 to 2012. Clinical parameters and outcome data were extracted. The specimens were stained for p53, Bcl-2, and p-glycoprotein. The results were analyzed for association with disease stage, International Prognostic Index (IPI), Prognostic Index for T-cell lymphoma (PIT), overall response rate (ORR), and overall survival (OS).*
Results: *Of eligible 159 patients (113 males, 46 females), median age was 53 years old. The histological subtypes included peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) 35.8%, angioimmunoblastic T-cell lymphoma (AITL) 18.2%, extranodal NK/T-cell lymphoma (ENKL) 17.0%, subcutaneous panniculitis-like T-cell lymphoma (SPTCL) 12.6%, cutaneous T-cell lymphoma (CTCL) 11.3%, anaplastic large cell lymphoma (ALCL) 4.4%, and enteropathy-associated T-cell lymphoma (EATL) 0.6%. Tissue samples were obtained for analysis in 135 patients. P53, Bcl-2, and p-glycoprotein were positive in 87%, 49%, and 28%, respectively. Median OS was 25 months. The expressions of p53, Bcl-2, and p-glycoprotein were not significantly correlated with advanced stage, high prognostic scores, ORR, and OS. However, Bcl-2 expression was statistically associated with histological subtypes. From Cox regression analyses, advanced stage, high prognostic scores, and histological subtypes were independent prognostic factors for OS.*
Conclusion: *The biomarker expressions varied in different types of PTCL and did not show any correlation with prognostic factors, ORR, or OS.*

Keywords: *P53, Bcl-2, P-glycoprotein, Peripheral T-cell lymphoma, Prognosis*

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Peripheral T-cell lymphoma (PTCL) is a heterogeneous entity composed of various histological subtypes and different prognosis. This lymphoid neoplasm is a rare type of non-Hodgkin lymphoma (NHL) and classified according to the World Health Organization (WHO) Classification of Hematopoietic and Lymphoid Neoplasms (2008)[1]. The incidence of PTCL is rare in Western countries; whereas, the number of patients is higher in Asian population. The incidence of PTCL in Thailand reported by the Thai Lymphoma Study Group was 10%[2].

Apoptotic pathways are known to be involved in the pathogenesis of lymphoid neoplasms including PTCL[3-6]. From previous studies, the expressions of p53 and Bcl-2 have been shown to be significantly associated with PTCL progression and clinical outcomes[7,8]. In addition, another reason for treatment failure is drug resistance. P-glycoprotein, which is involved in the resistance to several cytotoxic agents, was also demonstrated in PTCL[7,9]. Overall, the poor response of PTCL to standard chemotherapy may cause from these mechanisms. Nevertheless, the biological backgrounds and roles of these biological markers in clinical importance and prognosis have not been widely investigated. The purpose of the authors was to define the expressions of p53, Bcl-2, and p-glycoprotein and to associate with disease parameters, response to therapy, and survival outcomes of PTCL in Thai patients.

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Material and Method

The present study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (EC: 55-113-14-3-3).

The present study included the patients who were 15 years old or older and newly diagnosed as PTCL according to WHO classification (2008)[1] at Songklanagarind Hospital between January 2001 and December 2012. All histological slides at initial diagnosis were reviewed by hematopathologist (Kayasut K) based on the criteria according to WHO classification (2008). PTCL was diagnosed based on the histology and the expressions of T-cell antigens CD3 and T-cell-associated antigens CD4 or CD8, with an absence of pan B-cell antigens CD20 or CD79a. In case of inconclusive diagnosis, T-cell receptor (TCR) gamma was used for confirmation of monoclonality of the disease. Moreover, some subtypes may need specific markers for a definite diagnosis, for instance CD30 and ALK for anaplastic large cell lymphoma, CD56 and TIA1 for extranodal NK/T-cell lymphoma, nasal type. The available paraffin-embedded tissue samples at initial diagnosis of the patient were cut and immunohistolochemical stained for p53, Bcl-2, and p-glycoprotein.

Clinical information, treatment options, and treatment outcomes data of the patient were extracted from medical records including age, sex, extranodal presentation, B symptoms, performance status (PS) (ambulatory Eastern Cooperative Oncology Group [ECOG] PS 0-1 vs. non-ambulatory ECOG PS ≥2), Ann Arbor stage, lactate dehydrogenase (LDH) level, bone marrow (BM) involvement, prognostic scores, treatment options, treatment response, salvage therapy, and death. The prognostic scores in the present study used the International Prognostic Index (IPI)[10,11] and Prognostic Index for T-cell lymphoma (PIT)[12]. The patients were subdivided into two groups by IPI and PIT scoring system (low to low-intermediate IPI vs. high-intermediate to high IPI and PIT score 0-1 vs. score 2-4).

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 calling or checking the census records from the Hat Yai City Municipality.

One hundred fifty nine patients were recruited in the present study. Adequate tissue samples were obtained in 135 patients (84.9%).

Immunohistochemical study

Tumors samples, obtained by the tissue biopsy at the time of the initial diagnosis, were available to study in 135 cases. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue samples. The 2-μm-thick sections were cut on aminopropyltriethoxysilane-coated slides and were dried in a 60°C oven for 15 minutes. The sections were placed in the automated BOND-MAX system (Leica Biosystems) according to the following protocol. First, tissues were deparaffinized and pre-treated with the Epitope Retrieval Solution 2 (Tris-EDTA pH 8.9-9.1) at 98°C for 20 minutes. After washing steps, peroxidase blocking was carried out for 10 minutes using 3% hydrogen peroxide with stabilizers. Next, tissues were washed and then incubated with the primary antibody for 30 minutes, using p53 (DO-7, DAKO, Glostrup, Denmark, 1:300), Bcl-2 (Novocastra Laboratories, UK, 1:450), and p-glycoprotein (Novocastra Laboratories, UK, 1:50). Subsequently, slides were washed and developed with 3,3 diaminobenzidine tetrahydrochloride (DAB) for 10 minutes. Finally, hematoxylin was used as a counterstain, and then the slides were mounted.

Regarding the biomarker expression, scoring was analyzed in the area of highest protein expression as previously described[7]. 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 hematopathologist (Kayasut K) reviewed all initial histological slides as well as the immunohistochemical staining in the present study. The example of hematoxylin and eosin (H&E) and immunohistochemical staining specimens were shown in Fig. 1.

Statistical analysis

Statistical analysis was done using Stata Software Package, version 13.1. The clinical parameters and treatment outcomes data were compared among patients with or without expressions of these biomarkers using a Chi-square test. Univariate analysis of survival 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.

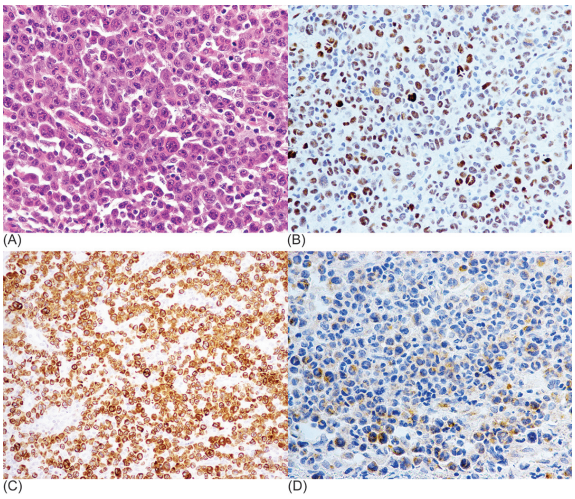

Fig. 1 The hematoxylin and eosin (H&E) and immunohistochemical staining in PTCL. Immunohistochemical detection showing (x400), (A) H&E staining, (B) strongly positive nuclear staining for p53 (4+), (C) strongly positive cytoplasmic staining for Bcl-2 (4+), (D) strongly positive cytoplasmic staining for p-glycoprotein (3+).

Results

Patient characteristics and treatment outcomes

One hundred fifty nine patients were recruited in the present study. The patient characteristics, treatment options, and treatment outcomes data were summarized in Table 1. Based on WHO classification, subtypes of PTCL were classified as peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) in 35.8%, angioimmunoblastic T-cell lymphoma (AITL) in 18.2%, extranodal NK/T-cell lymphoma (ENKL) in 17.0%, subcutaneous panniculitis-like T-cell lymphoma (SPTCL) in 12.6%, cutaneous T-cell lymphoma (CTCL) in 11.3%, anaplastic large cell lymphoma (ALCL) in 4.4%, and enteropathy-associated T-cell lymphoma (EATL) in 0.6% of cases. They were 113 males and 46 females (male to female ratio of 2.4:1). The median age was 53 years olds (range 16-89). The majority of the patients had good ECOG scores, low prognostic scores, elevated LDH level, and extranodal lesions. Fifty-five percent of the patients had Ann Arbor stage I-II. They were treated with CHOP regimen in 70% and radiotherapy in 17%. Of 123 patients evaluated, the overall response rate was 70% with 51% complete remission. Ninety patients (63%) died in the present study.

Table 1. Patient characteristics, treatment options, and treatment outcomes

Variables		No. of patients (%)
Sex	Male/female	113/46 (71/29)
Age (year)	Median (range)	53 (16-89)
	≤60	106 (67)
	>60	53 (33)
PS	ECOG 0-1	138 (87)
	ECOG 2-4	21 (13)
Histology	PTCL, NOS	57 (35.8)
	AITL	29 (18.2)
	ENKL	27 (17)
	SPTCL	20 (12.6)
	CTCL	18 (11.3)
	ALCL	7 (4.4)
	EATL	1 (0.6)
Stage	I-II	88 (55)
	III-IV	71 (45)
Extranodal	No	29 (18)
	Yes	130 (82)
LDH (IU/L)	Median (range)	697 (155-5,330)
	Higher than normal	96 (60)
IPI	L-LI	117 (74)
	HI-H	41 (26)
PIT	Score 0-1	97 (61)
	Score 2-4	61 (39)
Treatment	None	27 (17)
	CHOP	111 (70)
	Others	21 (13)
Radiotherapy	None	131 (83)
	Yes	27 (17)
Response	ORR	86 (70)
	CR	63 (51)
	PR	23 (19)
	SD	4 (3)
	PD	33 (27)
Salvage	No	104 (66)
	Yes	53 (34)
Death	No	52 (37)
	Yes	90 (63)

PS = performance status; ECOG = Eastern Cooperative Oncology Group; PTCL, NOS = peripheral T-cell lymphoma, not otherwise specified; AITL = angioimmunoblastic T-cell lymphoma; ENKL = extranodal NK/T-cell lymphoma, nasal type; SPTCL = subcutaneous panniculitis-like T-cell lymphoma; CTCL = cutaneous T-cell lymphoma; ALCL = anaplastic large cell lymphoma; EATL = enteropathy-associated T-cell lymphoma; LDH = lactate dehydrogenase; IPI = International Prognostic Index; L-LI = low to low-intermediate; HI-H = high-intermediate to high; PIT = Prognostic Index for T-cell lymphoma; CHOP = cyclophosphamide/doxorubicin/vincristine/prednisolone; ORR = overall response rate; CR = complete remission; PR = partial response; SD = stable disease; PD = progressive disease

The biomarker expressions

P53, Bcl-2, and p-glycoprotein positivity were demonstrated in 117 (87%), 66 (49%) and 38 (28%) patients, respectively. According to the histological subtypes, Bcl-2 was high expression in AITL at 71% and CTCL at 78%, and low expression in ENKL at 13% (p<0.001). The expressions of p53, Bcl-2, or p-glycoprotein were not significantly associated with advanced stage, high prognostic scores, and treatment response.

Survival analysis

Concerning survival with a median follow-up time of 18 months, the median survival was 25 months (Fig. 2). With univariate analyses, the expressions of p53, Bcl-2, and p-glycoprotein did not show prognostic significance on survival. The median survival of patients with p53 expression was 21.5 months compared to 34.0 months for those without expression (p = 0.562). The median survival of patients with Bcl-2 expression was 30.1 months compared to 20.6 months for those without expression (p = 0.284). Similarly, the median survival of patients with p-glycoprotein expression was 27.7 months compared to 25.1 months for those without expression (p = 0.723). Nevertheless, clinical stage (p<0.001), IPI (p<0.001), PIT (p<0.001), and histological subtypes (p<0.001) were statistically associated with survival. Among all of the histological subtypes, SPTCL and CTCL had better outcomes. From Cox regression analyses, a high IPI (p<0.001), a high PIT (p<0.001), and histological subtypes (p = 0.001) remained independent prognostic predictors for survival.

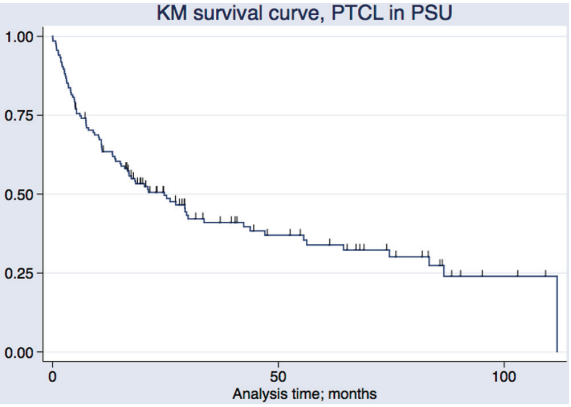

Fig. 2 Median overall survival of 159 PTCL patients from 2001-2012 in Songklanagarind Hospital (PSU).

Discussion

PTCL is a heterogeneous group of neoplasms with various clinical presentations and pathological features as outlined in the recently proposed WHO classification (2008). There are various treatment modalities in PTCL. Radiotherapy is applied for localized diseases. On the other hand, conventional chemotherapy (e.g., CHOP) regimens are used in disseminated diseases with produce disappointing results when compared with B-cell neoplasms. Therefore, biological factors are needed to investigate and identify the patients who might benefit from intensive therapeutic approaches.

Apoptotic pathways are known to be involved in the pathogenesis of lymphoid neoplasms including PTCL[3-6]. P53 is a nuclear phosphoprotein encoded by a tumor-suppressor gene. It plays a major role in the regulation of cellular stress response involving in cell cycle control, DNA repair, and apoptosis. Loss of p53 function or mutation may cause resistance to apoptosis[13]. Several investigators studied and defined the association of the biomarkers with the pathogenesis and prognosis of PTCL. Kanavaros et al reported that the proliferative activity was higher in p53 overexpression and Ki67 expression showed significant correlation with p53 overexpression in T-cell lymphomas[14]. In addition, Pescarmona et al also found that p53 expression was significantly associated with a poorer response to intensive chemotherapy in high-grade nodal PTCL[7].

Moreover, the role of Bcl-2 in the apoptotic pathway has been established[15]. Rassidakis et al reported that the Bcl-2 family proteins were expressed in a subset of PTCL and their levels correlated with apoptosis and proliferation of the PTCL[6]. Furthermore, recent study by Jung et al showed that Bcl-2 overexpression seemed to correlate with the progression of PTCL interacting with a p53-dependent pathway[8]. In addition to apoptotic pathway, another reason for treatment failure was drug resistance. One of the most important reasons that had been investigated is the multidrug resistance gene that encodes a p-glycoprotein[16]. The p-glycoprotein functions as an energy-dependent drug efflux pump and causes a reduction in intracellular drug concentration. It involved in the resistance to several cytotoxic agents, which were also demonstrated in PTCL[7,9].

PTCL accounted for 10% of all lymphoma in Thailand as the report by the Thai Lymphoma Study Group[2]. The present study submitted 159 cases from 2001 to 2012 with a diagnosis of PTCL according to

WHO classification 2008. The common PTCL subtypes were PTCL, NOS, AITL, and ENKL. Similar to other previous studies[7,8], they were middle-aged male, good ECOG scores, low IPI, and low PIT scores. Most of the patients in the present study had high LDH level and presented with extranodal lesions. They were treated with CHOP regimen in 70% and radiotherapy in 17%. The overall response rate was high as 70%; however, the median survival was dismal as 25 months. Sixty percent of the patients died in the present study.

The authors also investigated the expressions of p53, Bcl-2, and p-glycoprotein in the tissue specimens to define the association with survival outcomes. P53 positivity was detected in 87% of the cases, with Bcl-2 in 49%, and p-glycoprotein in 28%. The expressions of p53, Bcl-2, and p-glycoprotein were not correlated with advanced stage, high prognostic scores, and treatment response. Nevertheless, Bcl-2 expression was significantly associated with histological subtypes. It was high expression in AITL and CTCL, and low expression in ENKL. With multivariate analyses, a high IPI, a high PIT, and histological subtypes were significantly independent prognostic predictors for survival. Nevertheless, the biomarker expressions did not show any correlation. These results were difference from the previous studies, reported that p53 and Bcl2/p53 expressions were associated with PTCL survival[7,8].

Since the authors recruited a high number of patients with various pathological subtypes, the results should represent a whole group of PTCL patients in southern Thailand when compared with other studies. The other explanations for different findings might cause from a difference in the proportion of PTCL subtypes, ethnicity, genetics, and environmental settings e.g., economic status, prevalence of Epstein-Barr virus infection as well as various modalities of treatment including supportive cares.

Conclusion

PTCL predominantly presented in middle-aged male with low prognostic scores. They were responded well to standard chemotherapy; however, the median overall survival of these patients was disappointing. The authors could not confirm that the biomarkers, p53, Bcl-2, and p-glycoprotein were related with disease severity, treatment response, and survival outcomes in patients with PTCL. Therefore, a large number of patients, subtype analyses, and the other biomarker expressions should be further investigated.

What is already known on this topic?

Apoptotic pathways are involved in the pathogenesis of PTCL. P53 and Bcl-2 have been shown to be significantly associated with PTCL progression and prognosis. P-glycoprotein also involved in the resistance to several cytotoxic agents in PTCL.

What this study adds?

P53, Bcl-2, and p-glycoprotein were not related with disease severity, treatment response, and survival outcomes in Thai patients with PTCL. However, Bcl-2 expression was significantly associated with PTCL subtypes. In addition, advanced stage, high prognostic scores, and histological subtypes were independent prognostic predictors for survival in the present study.

Acknowledgement

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Potential conflicts of interest

None.

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การแสดงออกของสารโปรตีน p53, Bcl-2 และ p-glycoprotein และความสัมพันธ์กับการพยากรณ์โรคในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด peripheral T-cell lymphoma (PTCL)

จักราวดี จุฬามณี, คณิตา กายะสุต, อานุภาพ เลขะกุล

วัตถุประสงค์: เพื่อศึกษาความถี่ของการแสดงออกของสารโปรตีน p53, Bcl-2 และ p-glycoprotein และความสัมพันธ์ระหว่างการแสดงออกของสารโปรตีนกับการพยากรณ์โรคในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด peripheral T-cell lymphoma (PTCL)

วัสดุและวิธีการ: ศึกษาผู้ป่วยใหม่ที่ได้รับการวินิจฉัยเป็นโรคมะเร็งต่อมน้ำเหลืองชนิด PTCL ตั้งแต่เดือนมกราคม พ.ศ. 2544 ถึง ธันวาคม พ.ศ. 2555 จากเวชระเบียนผู้ป่วยนอกโรงพยาบาลสงขลานครินทร์ โดยเก็บข้อมูลพื้นฐานทางคลินิกและผลการรักษาของผู้ป่วยร่วมกับนำชิ้นเนื้อที่ได้รับการวินิจฉัยมาย้อมโดยวิธี immunohistochemistry เพื่อตรวจการแสดงออกของสารโปรตีน p53 Bcl-2 และ p-glycoprotein นำผลการตรวจที่ได้มาวิเคราะห์เพื่อหาความสัมพันธ์กับระยะโรค International Prognostic Index (IPI) Prognostic Index for T-cell lymphoma (PIT) การตอบสนองต่อการรักษาและอัตราการรอดชีวิต

ผลการศึกษา: มีผู้ป่วยทั้งหมด 159 ราย เป็นผู้ป่วยชาย 113 ราย ผู้ป่วยหญิง 46 ราย มัธยฐานของอายุเท่ากับ 53 ปี เมื่อจำแนก PTCL ตามชนิดย่อยพบ peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) ร้อยละ 35.8 angioimmunoblastic T-cell lymphoma (AITL) ร้อยละ 18.2 extranodal NK/T-cell lymphoma (ENKL) ร้อยละ 17.0 subcutaneous panniculitis-like T-cell lymphoma (SPTCL) ร้อยละ 12.6 cutaneous T-cell lymphoma (CTCL) ร้อยละ 11.3 anaplastic large cell lymphoma (ALCL) ร้อยละ 4.4 และ enteropathy-associated T-cell lymphoma (EATL) ร้อยละ 0.6 มีชิ้นเนื้อที่เพียงพอสำหรับการย้อมสารโปรตีนจำนวน 135 ราย พบการแสดงออกของ p53 Bcl-2 และ p-glycoprotein คิดเป็นร้อยละ 87, 49 และ 28 ตามลำดับ มัธยฐานของระยะเวลารอดชีวิตของผู้ป่วยในการศึกษาเท่ากับ 25 เดือน จากการวิเคราะห์พบว่าการแสดงออกของสารโปรตีน p53, Bcl-2 และ p-glycoprotein ไม่มีความสัมพันธ์กับระยะของโรค ดัชนีพยากรณ์โรคที่ไม่ดี การตอบสนองต่อการรักษา และอัตราการรอดชีวิตของผู้ป่วย อย่างไรก็ตามพบว่าการแสดงออกของสาร Bcl-2 มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับชนิดย่อยของ PTCL จากการวิเคราะห์ตัวแปรพหุพบว่าระยะรุนแรงของโรค ดัชนีพยากรณ์โรคที่สูง และชนิดย่อยของ PTCL เป็นปัจจัยอิสระที่สามารถพยากรณ์อัตราการรอดชีวิตของผู้ป่วย PTCL ได้อย่างมีนัยสำคัญทางสถิติ

สรุป: สารโปรตีน p53 Bcl-2 และ p-glycoprotein มีอัตราการแสดงออกหลากหลายในชนิดย่อยของ PTCL และไม่พบความสัมพันธ์ของสารโปรตีนดังกล่าวต่อดัชนีพยากรณ์โรค การตอบสนองต่อการรักษา และอัตราการรอดชีวิตของผู้ป่วย