Original Article

The Expression of p53 and Survival of Extranodal NK/T-Cell Lymphoma, Nasal Type (ENKL) in Thai Patients

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Abstract:

Objective: *To determine the association between p53 expression and disease parameters, treatment responses, and survival of Thai patients with extranodal NK/T-cell lymphoma, nasal type (ENKL).* ***Materials and Methods:*** *Adult patients with ENKL at Songklanagarind Hospital from 2001 to 2012 were reviewed. Clinical parameters and outcome data were extracted. The available pathological specimens were immunochemically stained for p53. The results were analyzed for association with disease stage, prognostic scores, treatment responses, and overall survival.* ***Results:*** *Twenty-four patients (17 males and 7 females) were included for the study. The median age was 52 years. Most patients were under 60 years old (71%), had ECOG scores 0-1 (92%), stage I-II (92%), low to low-intermediate International Prognostic Index (IPI) (92%), and low Prognostic Index for PTCL, NOS (79%). All patients presented with extranodal lesions, most commonly nasal lesions (83%). Seventy percent of patients were treated with chemotherapy, predominantly (94%) CHOP regimen and 54% percent with radiotherapy, alone or as concurrent chemo-radiation. Of 18 evaluable patients, the overall response rate was 67%, with 56% complete response. The p53 expression is detected in 92% of tumors and significantly correlated with limited stage and low IPI. The median overall survival (OS) was 16.8 months. Advanced stage, high IPI, radiotherapy, and response to treatment, but not p53 expression, are associated with lower OS. With Cox regression analysis, radiotherapy and response to treatment were independent prognostic predictors for survival.* ***Conclusion:*** *p53 is commonly expressed in ENKL and significantly associated with limited stage and low IPI. Radiotherapy and response to treatment were predictors for survival.*

Keywords : ● *Extranodal NK/T-cell lymphoma* ● *Nasal type* ● *Survival* ● *p53*

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Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKL) is a highly aggressive disease with a grave prognosis. It usually presents with extranodal lesions primarily in the nasal cavity, nasopharynx, and paranasal sinuses. However, widespread lesions can occur at various sites most often with skin, lung, and gastrointestinal tract dissemination.[1,2] ENKL is characterized by vascular damage, prominent necrosis with bony destruction, cytotoxic phenotype, and is associated with the Ebstein-Barr virus (EBV).[1] From a recent report by the International T-cell lymphoma project, ENKL is a rare tumor in Western countries accounting for 4.3% in Europe and 5.1% in North America with

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a greater prevalence in Asian countries in 22.4% of all peripheral T-cell lymphoma (PTCL) patients.[3] The incidence in Thailand reported by the Thai Lymphoma Study Group was 25% of all PTCL.[4]

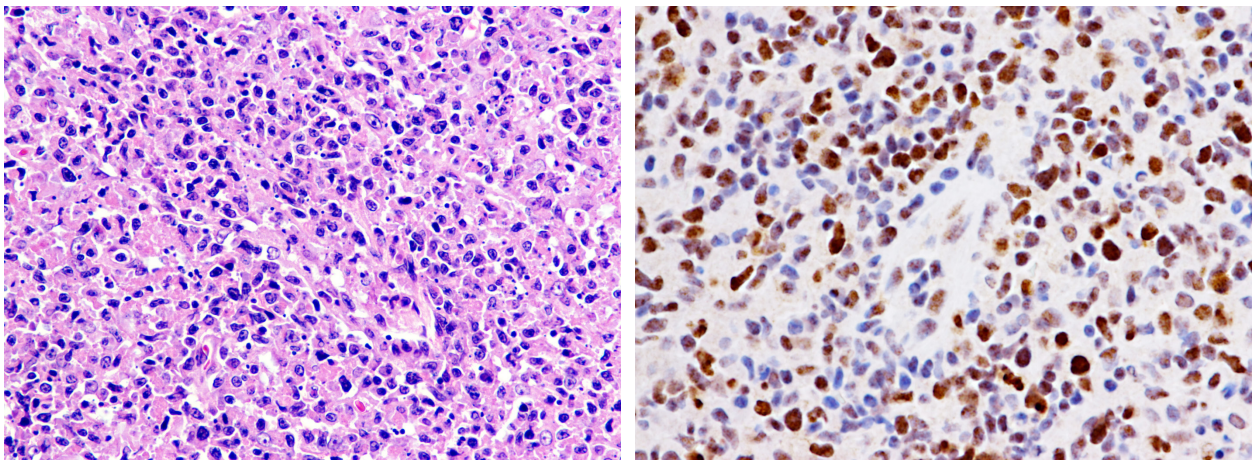
At present, there are various treatment strategies for ENKL; however, they produce unsatisfactory outcomes. Therefore, the biological factors that might be involved in the treatment outcomes and prognosis of ENKL need to be investigated and identified. Several investigators have studied apoptotic pathways and found the involvement in the pathogenesis of lymphoid neoplasms including PTCL.[5-8] The role of p53 as a prognostic factor of ENKL was reported as well; however, the results remain uncertain.[9-11] The purpose of this study was to define the expression of p53 as well as to correlate the findings with the disease parameters, treatment responses, and survival of Thai patients with ENKL.

Materials and Methods

Adult patients aged 15 years and older with a diagnosis of extranodal NK/T-cell lymphoma, nasal type according to WHO classification 2008[1] at Songklanagarind Hospital between January 2001 and December 2012 were retrospectively review. All in every case, the paraffin-embedded specimen from tissue at onset was available for morphological and immunological investigation. The diagnosis of ENKL was based on the histologic and immunophenotypic features. Immunohistochemical staining was 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.

P53 was assessed by immunohistochemical analysis on formalin-fixed paraffin-embedded tissue sections using monoclonal antibodies of p53 (DO-7, DAKO, Glostrup, Denmark, 1:300) 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: 0 (completely negative reactions), 1+ (< 10% of positive cells), 2+ (10-50% of positive cells), 3+ (51-90% of positive cells), and 4+ (> 90% positive cells). The cases that exhibited a majority of positive tumor cells (> 10% or ≥ 2+ positivity) were considered as positive expression. The H&E and immunohistochemical staining results are shown in Figure 1.

The clinical parameters and treatment outcomes were reviewed from medical records. Extracted data included age, sex, clinical presentation, performance status (PS), clinical stage, lactate dehydrogenase (LDH) level, prognostic scores, treatment options, response to treatment, salvage therapy, and death.



(a) (b)

Figure 1 NK/T-cell lymphoma, nasal type (a), H&E, p53 expression (nuclear immunoreactivity) (b)

The Ann Arbor staging system was used for disease staging in this study. In addition, this study also used the International Prognostic Index (IPI) and Prognostic Index for PTCL, not otherwise specified (NOS) (PIT score) as prognostic scores. The IPI score consists of Ann Arbor stage, extranodal involvement, age, LDH level, and PS.[12] The patients were classified into two groups of IPI: low to low-intermediate IPI and high-intermediate to high IPI. Regarding the PIT score, it consists of age, PS, LDH level, and bone marrow involvement.[13] The patients were categorized into two groups of PIT score: score 0-1 and score 2-4.

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, according to death certificates issued by a physician stating the cause of death. All living patients were confirmed directly by phone call, mail or checking the census records at the Hat Yai Municipality Office.

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 expression of p53 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. 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.

Results

Patient characteristics and treatment outcomes

Twenty-four patients were recruited and analyzed in this study. There were 17 males and 7 females, giving a male to female ratio of 2.4:1. The median age was 52 years old (range 24-79). Most patients were under 60 years old (70.8%), good ECOG scores (91.7%), Ann Arbor stage I-II (91.7%), low to low-intermediate IPI (91.7%), and low PIT scores (79.2%). All patients presented with extranodal lesions, mainly with nasal masses (83.3%) and none of them had bone marrow involvement. Of 24 patients evaluated, 17 patients (70.8%) were treated with chemotherapy. Of those, CHOP regimen was used in 16 patients (94.1%), and one with Hyper-CVAD regimen. Fifty-four percent of 24 patients were treated with the involved-field radiation. In addition, 10 from total 20 treated patients received concurrent chemo-radiation. Treatments were completed in 18 of 24 patients (75%) with an ORR of 66.7% and the CR rate was 55.6%. The patient characteristics, treatment options, and treatment outcomes are summarized in Table 1.

The p53 expression

P53 positivity was demonstrated in 22 (91.7%) patients and significantly correlated with limited stage ($p = 0.026$) and low IPI ($p = 0.026$). The details are demonstrated in Table 2.

Survival analysis

With a median follow-up time of 14 months, the median overall survival was 16.8 months (Figure 2). Fourteen patients (58%) died in this study. The most common cause of death was disease progression (64%). Projected 3-year OS and 5-year OS were 45% and 37.5%, respectively. With univariate analysis, advanced stage ($p = 0.015$), high IPI ($p = 0.015$), radiotherapy ($p = 0.002$), and response to treatment ($p = 0.002$) significantly affected OS (Figure 3). Nevertheless, p53 expression did not show prognostic significance on survival. With Cox regression analysis, radiotherapy ($p = 0.020$) and response to treatment ($p = 0.002$) were independent prognostic predictors for survival in this study.

Table 1 Patient characteristics, treatment options, and treatment outcome of 24 patients with ENKL

Variables		No of patients (%)	Variables		No of patients (%)
Sex	Male/Female	17/7 (71:29)	No treatment		4 (17)
Age, years	Median (range)	52 (24-79)	Treatment		20 (83)
	≤ 60	17 (71)	Chemotherapy	CHOP	16 (94)
	> 60	7 (29)		HyperCVAD	1 (6)
PS	ECOG 0-1	22 (92)	Radiotherapy		13 (54)
	ECOG 2-4	2 (8)	Treatment modality		
Stage	I-II	22 (92)	CMT		7 (35)
	III-IV	2 (8)	RT		3 (15)
Primary site	Nasal	20 (83)	CMT + RT		10 (50)
	Oropharynx	1 (4)	Response	ORR	12/18 (67)
	Orbit	2 (8)		CR	10/18 (56)
	Skin	1 (4)		PR	2/18 (11)
LDH	> normal	14 (58)		SD	1/18 (5)
IPI	L-LI	22 (92)		PD	5/18 (28)
	HI-H	2 (8)	Salvage therapy		6 (25)
PIT	Score 0-1	19 (79)	Death		14 (58)
	Score 2-4	5 (21)	Cause of death	Disease progression	9 (64)
				Infection	1 (7)
				Others	4 (29)

CHOP, cyclophosphamide/doxorubicin/vincristine/prednisolone; CR, complete remission; ECOG, eastern cooperative oncology group; HyperCVAD, cyclophosphamide/vincristine/prednisolone/dexamethasone; HI-H, high-intermediate to high; IPI, international prognostic index; LDH, lactate dehydrogenase; L-LI, low to low-intermediate; ORR, overall response rate; PD, progressive disease; PIT, prognostic index for peripheral T-cell lymphoma; PR, partial response; PS, performance status; SD, stable disease

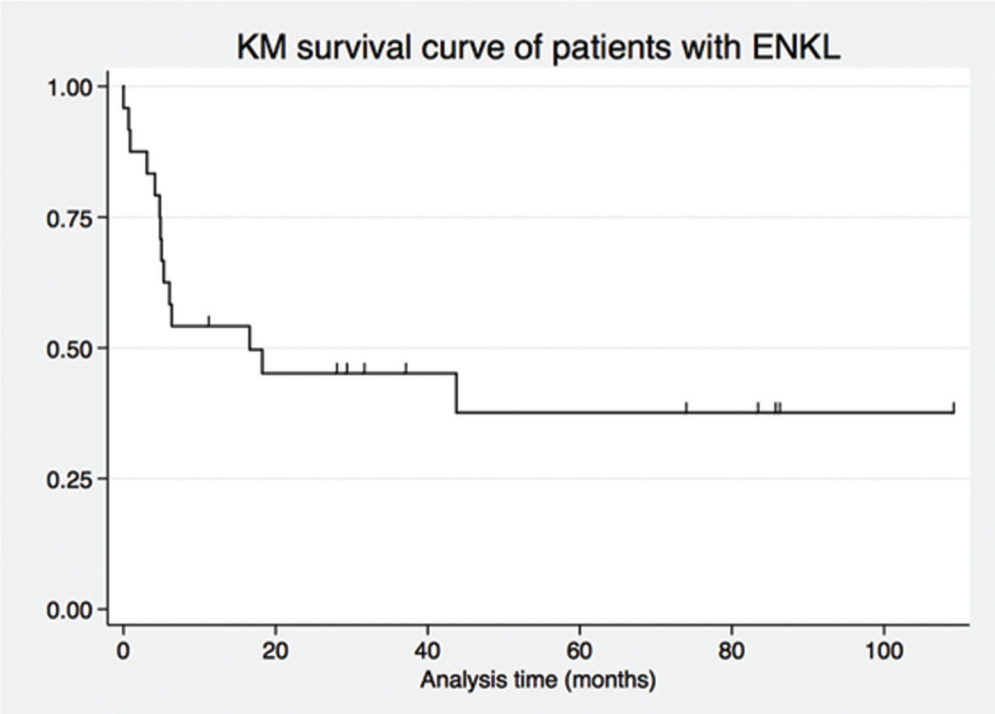


Figure 2 Overall survival of patients with ENKL

Table 2 P53 positivity and the relationship to clinical parameters in 22 ENKL patients

Variables	No of patients (%)	*p* value
Sex		
Male	15 (68)	0.343
Female	7 (32)	
Age		
≤ 60	15 (68)	0.343
> 60	7 (32)	
PS		
ECOG 0-1	20 (91)	0.656
ECOG 2-4	2 (9)	
Ann Arbor stage		
I-II	21 (95)	0.026
III-IV	1 (5)	
LDH		
Normal	9 (41)	0.803
> Normal	13 (59)	
IPI		
L-LI	21 (95)	0.026
HI-H	1 (5)	
PIT		
Score 0-1	17 (77)	0.449
Score 2-4	5 (23)	

ECOG, Eastern Cooperative Oncology Group; HI-H, high-intermediate to high; IPI, international prognostic index; LDH, lactate dehydrogenase; L-LI, low to low-intermediate; PIT, prognostic index for peripheral T-cell lymphoma; PS, performance status

Discussion

ENKL is more prevalent in Asian populations including Thai patients according to the report by the Thai Lymphoma Study Group.[3,4] It predominantly affects male adults and most of the patients present with destructive midline lesion, especially nasal masses.[2,9,11,14] Although there are various treatment strategies for ENKL nowadays, the treatment and survival outcomes of this entity remains disappointing.[2,4,9,11,14] Recently, the apoptotic pathways have been investigated to identify the treatment outcome and survival in PTCL patients.[5-8]

p53 is a nuclear phosphoprotein encoded by a tumor suppressor gene located on chromosome 17p13. P53 plays a major role in regulation of cellular stress response, in part through the transcriptional activation of genes involved in cell cycle control, DNA repair, and apoptosis. Loss of p53 function may cause resistance to apoptosis.[15] Previous studies of p53 in PTCL reported that p53 overexpression significantly associated with poorer response to intensive chemotherapy and survival.[7,8] The role of p53 in ENKL was also reported. A study from China by Ye et al reported the association of p53 expression with tumor stage and high IPI. Moreover, they also demonstrated p53 expression as an independent prognostic factor for survival from Cox regression test.[9] On the contrary, a study from Singapore by Ng et al did not show any association of p53 expression on tumor stage and survival.[11] This study is aimed to define the expression of p53 and its prognostic impact on survival in Thai patients with ENKL.

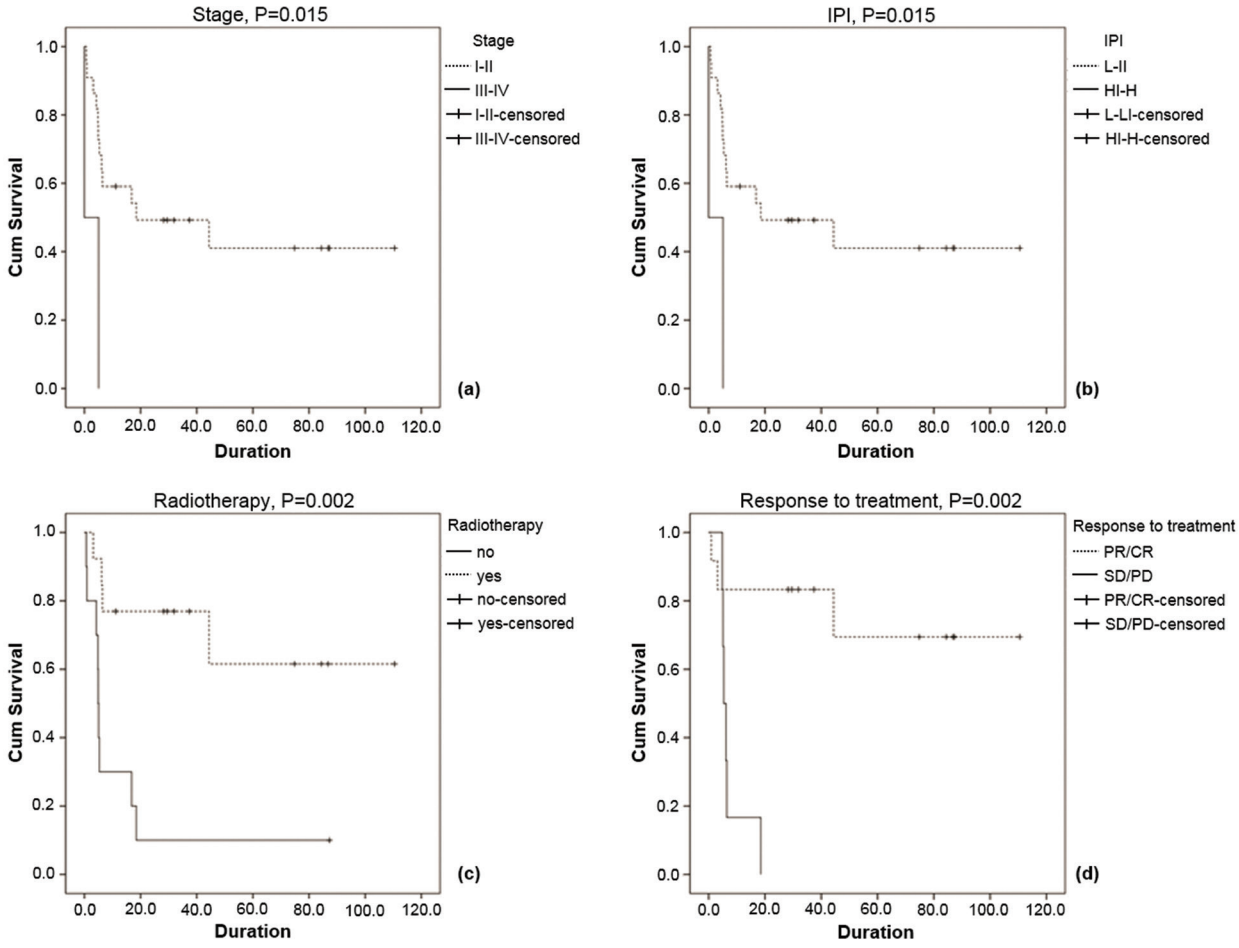


Figure 3 Effects of Ann Arbor stage (a), IPI (b), radiotherapy (c), and response to treatment (d) on overall survival of patients with ENKL

Twenty-four patients were reviewed in this study. ENKL predominantly affected middle-aged males. Most of the patients presented with nasal masses and had a limited stage of disease. The majority of the cases were treated with CHOP regimen and radiotherapy. Furthermore, 50% of the treated cases received combined chemo-radiation. However, only half of the patients achieved complete remission. The results from current studies were compared with this study as shown in Table 3. The patient characteristics, disease parameters, and treatment modalities were comparable; however, there were no report of the treatment outcomes from the previous studies.[9,11] Regarding the biomarker expression, p53 positivity was demonstrated in 92% of the patients and was associated with limited stage and low IPI which was different to the previous report by Ye et al.[9] The different findings may cause from a low number of patients in this study and the variable of p53 positivity cut-off value.

Fifty-eight percent of the patients died in this study. The most common cause of death was disease progression. The median overall survival was 16.8 months and the projected 3-year OS and 5-year OS rates were 45% and 37.5%, respectively. The survival outcome was comparable with the report by the International T-cell Lymphoma Project; 5-year OS and 5-year failure-free survival rates were 42% and 29%, respectively.[3] According to our knowledge, combined chemotherapy-radiotherapy is a standard treatment in ENKL nowadays.

Table 3 Clinical comparisons with previous studies

Variables	This study (n = 24)	Ye et al, 2013[9] (n = 84)	Ng et al, 2004[11] (n = 42)
M:F ratio	2.4:1	2:1	4.25:1
Median age (years)	52	45	44
LDH > normal (%)	58	75	56
Primary site of involvement (%)			
Nasal cavity and oro-nasopharynx	87	83.3	74
Orbit	8	-	-
GI	-	3.6	7
Lung	-	3.6	-
Skin	4	2.4	12
Testis	-	-	5
Brain	-	-	2
Ann Arbor Stage I-II (%)	92	86.4	82
IPI 0-1 (%)	92	35	60
p53 expression (%)	91.7	33.3	40.5
Treatment (%)			(30 patients)
None	17	-	10
Chemotherapy	71	-	86.7
Radiotherapy	54	-	23.3
Death (%)	58	-	79
Overall survival	Median 16.8 months Median follow-up time 14 months	54.7% patients were alive at median follow-up time 14 months	-
Conclusions	p53 was associated with limited stage (p = 0.026) and low IPI (p = 0.026). OS was associated with advanced stage (p = 0.015), high IPI (p = 0.015), radiotherapy (p = 0.002), and response to treatment (p = 0.002). Cox regression test showed radiotherapy (p = 0.020) and response to treatment (p = 0.002) were independent prognostic factors	p53 was associated with tumor stage (p = 0.016) and high IPI (p = 0.026). Cox regression test showed p53 expression rate (p = 0.002) and IPI (p = 0.016) were independent prognostic factors.	p53 was not associated with advanced stage and OS.

F, female; GI, gastrointestinal; IPI, international prognostic index; LDH, lactate dehydrogenase; M, male; OS, overall survival

Anthracycline-based regimens produce unsatisfactory outcomes. Furthermore, L-asparaginase-based chemotherapy was found to be effective for NK/T-cell lymphoma treatment, and now L-asparaginase has been incorporated into several regimens. Fifty percent of the treated cases in this study received combined chemoradiation; however, most of them were treated with CHOP regimen. That might affect the treatment outcomes and overall survival of the patients in this study.

According to univariate analysis, advanced stage of disease, high IPI score, radiotherapy, and response to treatment significantly affected survival. Nevertheless, the p53 expression did not show prognostic significance on survival. This finding differed from the report by Ye et al.[9] Furthermore, Cox regression analysis showed that radiotherapy and response to treatment remained statistically independent prognostic predictors for ENKL patients. These results suggested that radiotherapy should be incorporated into the ENKL treatment, particularly in the limited stage of disease.

Summary

ENKL predominantly presented with extranodal lesions mainly in the nasal cavity. Most patients were middle-aged males with limited stage of disease and low prognostic scores. Only half of the patients responded well to chemotherapy and radiation. P53 was highly detected in the tumor cells and seemed to be involved in the pathogenesis of this entity. However, the effect of p53 on survival was not confirmed in this study. Since our study enrolled a low number of patients, that might have caused different results when compared with other studies. Therefore, a large number of patients and other biomarker expressions are needed for further investigation to facilitate the diagnosis and to develop other effective treatment modalities for ENKL patients.

Acknowledgement

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การแสดงออกของ p53 และความสัมพันธ์กับการพยากรณ์โรคในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด Extranodal NK/T-cell Lymphoma, Nasal Type (ENKL)

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บทคัดย่อ

วัตถุประสงค์ *เพื่อศึกษาอัตราการแสดงออกของ p53 และผลของการแสดงออกที่มีต่อการพยากรณ์โรคและอัตราการรอดชีวิตในผู้ป่วยคนไทยที่เป็นมะเร็งต่อมน้ำเหลืองชนิด ENKL* ***วัสดุและวิธีการ*** *ศึกษาผู้ป่วยผู้ใหญ่ที่ได้รับการวินิจฉัยโรคมะเร็งต่อมน้ำเหลืองชนิด ENKL ที่โรงพยาบาลสงขลานครินทร์ย้อนหลังตั้งแต่ พ.ศ. 2544-2555 โดยเก็บข้อมูลพื้นฐานทางคลินิกและผลการรักษาของผู้ป่วยจากเวชระเบียน ร่วมกับศึกษาการแสดงออกของ p53 ในชิ้นเนื้อที่ย้อมเพิ่มเติมด้วยวิธี immunohistochemistry นำผลของการแสดงออกมาวิเคราะห์เพื่อหาความสัมพันธ์กับระยะโรค ปัจจัยการพยากรณ์โรคอัตราการตอบสนองต่อการรักษาและอัตราการรอดชีวิต* ***ผลการศึกษา*** *ผู้ป่วยในการศึกษาทั้งหมด 24 ราย (ชาย 17 รายและหญิง 7 ราย) ค่ามัธยฐานของอายุเท่ากับ 52 ปี ผู้ป่วยส่วนใหญ่มีอายุน้อยกว่า 60 ปี (ร้อยละ 71) คะแนน ECOG 0-1 (ร้อยละ 92) โรคอยู่ในระยะที่ 1 และ 2 (ร้อยละ 92) low - low-intermediate IPI (ร้อยละ 92) และ low PIT score (ร้อยละ 79) ผู้ป่วยทุกรายมีอาการแสดงของตัวโรคนอกต่อมน้ำเหลือง โดยร้อยละ 83 มาด้วยอาการก้อนในโพรงจมูก ผู้ป่วยร้อยละ 70 ได้รับการรักษาด้วยยาเคมีบำบัด (CHOP regimen ร้อยละ 94) และร้อยละ 54 ได้รับการฉายรังสี มีผู้ป่วย 18 รายที่สามารถประเมินการตอบสนองพบว่าอัตราการตอบสนองต่อการรักษาคิดเป็นร้อยละ 67 และอัตราโรคสงบร้อยละ 56 อัตราการแสดงออกของ p53 คิดเป็นร้อยละ 92 และการแสดงออกของ p53 สัมพันธ์กับระยะจำกัดของโรคและ IPI ต่ำ มัธยฐานของระยะเวลารอดชีวิต 16.8 เดือน ปัจจัยที่มีความสัมพันธ์กับการรอดชีวิตอย่างมีนัยสำคัญทางสถิติ ได้แก่ ระยะของโรค IPI, การรักษาด้วยการฉายรังสี และการตอบสนองต่อการรักษา แต่การแสดงออกของ p53 ไม่สัมพันธ์กับการรอดชีวิตหรือการพยากรณ์โรคของผู้ป่วย การรักษาด้วยการฉายรังสีและการตอบสนองต่อการรักษาเป็นปัจจัยที่ส่งผลต่อการพยากรณ์โรคอย่างมีนัยสำคัญทางสถิติ* ***สรุป*** *มะเร็งต่อมน้ำเหลืองชนิด ENKL มีอัตราการแสดงออกของ p53 สูงและสัมพันธ์กับระยะจำกัดของโรคและ IPI ต่ำ การรักษาด้วยการฉายรังสีและการตอบสนองต่อการรักษาเป็นปัจจัยที่ส่งผลต่อการพยากรณ์โรคอย่างมีนัยสำคัญทางสถิติ*

Keywords : ● *Xtranodal NK/T-cell lymphoma* ● *Asal type* ● *Urvival* ● *p53*
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