Original Article

The Prevalence of CD30 Expression and Relationship to Survival in Patients with Peripheral T-Cell Lymphoma (PTCL)

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Objective: To define the prevalence of CD30 expression and the relationship to survival in patients with peripheral T-cell lymphoma (PTCL).

Materials and Methods: A 12-year retrospective study of 135 PTCL patients was completed. Their tissue specimens were stained for CD30 antibody and the results were correlated with clinical data and survival.

Results: One hundred thirty-five patients were enrolled. The subtypes of PTCL were classified as PTCL-NOS (36.3%), nasal NKTCL (17.8%), AITL (15.6%), CTCL (13.3%), SPTCL (11.1%), ALCL (4.4%), C-ALCL (0.7%), and EATL (0.7%). The expression of CD30 in the PTCLs was 34.8%, which significantly associated with histological subtypes ($p<0.001$). There was a higher prevalence in ALCL or C-ALCL (100.0%), nasal NKTCL (79.2%), and PTCL- NOS (30.6%). The median survival was 25 months with a projected 5-year survival of 37.0%. CD30 positivity was significantly associated with poor survival outcome ($CD30^-$ 30 months versus $CD30^+$ 14 months, $p=0.013$). From Cox regression analysis, PTCL subtypes were independent prognostic predictor for survival in the present study.

Conclusion: The expression of CD30 in PTCLs was demonstrated in one-third of patients and was associated with histological subtypes and inferior survival outcome.

Keywords: CD30, Survival, Peripheral T-cell lymphoma

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Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare non-Hodgkin's lymphoma (NHL) entities that are composed of various histological subtypes and different outcomes. PTCLs are classified according to the World Health Organization (WHO) 2008 classification of hematopoietic and lymphoid neoplasms[1] with a recent revision in 2016. In Western countries, PTCLs account for 5.0% to 10.0% of all NHL[2-4] while the prevalence is higher in Asian countries with approximately 15.0% to 20.0% of all lymphomas[3-5]. In Thailand, the incidence of PTCLs was reported by Bunworasate et al as 10.0% of all NHL[5].

PTCLs predominantly present in males with advanced stage and symptomatic disease[6-12]. At present, there are limited active agents in both front-line and second-line treatment for PTCL patients. Most of them received anthracycline-based combination chemotherapy; however, it was associated with dismal outcomes[4,7,9,10]. The five-year overall survival (OS) rates were poor, ranging from 7.0% to 90.0% according to PTCL subtypes, from the report by the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study[4]. Therefore, the novel biomarkers that might be involved in the pathogenesis of PTCLs need to be investigated.

CD30 antigen is a member of the tumor necrosis factor receptor (TNFR) superfamily[13]. It was initially described in 1982 as an antigen expressed on Hodgkin's disease associated molecules[14]. A subsequent study revealed CD30 variable expression on several NHL. This persisted in anaplastic large cell lymphoma (ALCL)[15]. Cross-linking of CD30 and its ligand (CD30L) activate the nuclear factor-κB (NF-κB) pathway mediated by TNFR-associated

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factor proteins. The NF-κB activation can lead to pleiotropic effects on cell growth and survival[16]. In recent years, several studies on CD30 expression in PTCL subtypes reported a variable number of CD30 expressions[6-12,17]. In addition, the efficacy of conjugated antiCD30 antibodies (brentuximab vedotin) have been investigated and gave promising outcomes in both front-line and relapsed or refractory PTCL treatments[18-21]. The present study aimed to identify the prevalence of CD30 expression and the clinical correlation on survival in PTCL patients. The results could be used to assess the feasibility of novel targeted immunotherapy in PTCLs.

Materials and Methods

The research protocol of the present study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (EC 56-488-14-1).

Case selection and clinical data collection

One hundred thirty-five patients were enrolled between January 2001 and December 2012. The eligibility criteria were patients who were 15 years old and older with fulfilled the criteria for a diagnosis of PTCL according to WHO classification 2008[1]. In every case, the paraffin-embedded specimen from tissues at onset were available for further investigation. The data included age, gender, clinical presentation, performance status (PS) using ambulatory Eastern Cooperative Oncology Group (ECOG) score to differentiate ECOG PS 0 to 1 versus non-ambulatory ECOG PS of 2 or more, the Ann arbor stage, lactate dehydrogenase (LDH) level, bone marrow (BM) involvement, the prognostic scores, treatment options, response of treatment, salvage therapy, and death as well as the follow-up information were retrospectively reviewed from the medical records. Regarding the prognostic scores, the present study used the International Prognostic Index (IPI), Prognostic Index for T-cell lymphoma (PIT), and International Peripheral T-Cell Lymphoma Project score (IPTCLP)[22-24]. All living patients were confirmed directly at the outpatient clinic or by phone call, mail or checking the census records at the Hat Yai Municipality Office. All deaths were confirmed by the medical records and the registered of death certificates issued by a physician stating the cause of death from the Department of Provincial Administration, Ministry of Interior.

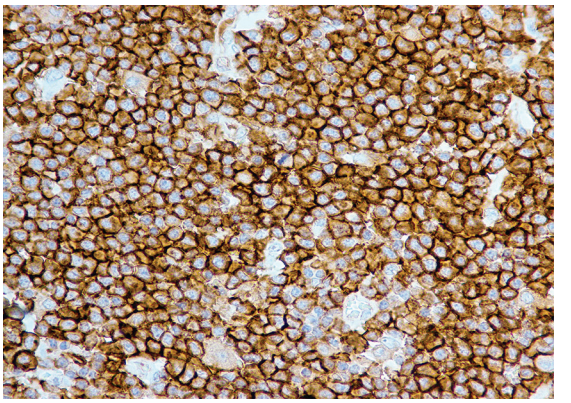

Figure 1. Immunoreactivity for CD30 of the tumor cells.

Histopathological and immunohistochemical assessment

The paraffin-embedded tissues at the onset of diagnosis were available to evaluate in all cases. The histological slides of all cases were reviewed to confirm the diagnosis of PTCLs based on their morphological and immunohistochemical staining using the antibodies against T-, B-, and natural killer (NK)-cell differentiation antigens including CD3, CD4, CD5, CD8, CD20, CD30, CD56, CD79a, and TIA-1. In addition, T-cell receptor gamma gene rearrangement was performed in some inconclusive cases to confirm the clonality of disease.

The available paraffin-embedded tissues were further recut and stained for monoclonal antibodies of CD30 (Ber-H2, DAKO, 1:100) by using the automated Leica BOND-MAX system (Leica Biosystems). CD30 expression was semi-quantitatively scored as follows: 0 (completely negative reactions), 1+ (less than 25.0% of positive cells), 2+ (25.0% to 50.0% of positive cells), 3+ (51.0% to 75.0% of positive cells), and 4+ (more than 75.0% of positive cells) in the area of highest protein expression. The cases that exhibited 25.0% or more, or 2+ or more positivity of tumor cells, were considered as positive expression[17]. All initial histological slides and immunohistochemical staining specimens in the present study were reviewed and assessed by the hematopathologist (Kayasut K). The representative CD30 staining results are shown in Figure 1.

Statistical analysis

Statistical analysis was performed using Stata, version 13.1 (StataCorp LP, College Station, TX, USA). The continuous data were presented as mean or median with range. Categorical data were presented as number and percentage, and differences of clinical

data and treatment outcomes among patients with or without expression of CD30, were assessed by a Chi-square test. OS was calculated as the time interval from the date of diagnosis to the date of death or last follow-up. Survival times were analyzed by the Kaplan-Meier method and a log-rank test. Multivariate analyses for OS were performed using a Cox regression model. Differences were considered statistically significant when p-value was less than 0.05.

Results

Of the 135 eligible cases submitted, subtypes of PTCL were classified as PTCL, not otherwise specified (NOS) in 36.3%, extranodal NK/T-cell lymphoma, nasal type (nasal NKTCL) in 17.8%, angioimmunoblastic T-cell lymphoma (AITL) in 15.6%, cutaneous T-cell lymphoma (CTCL) in 13.3%, subcutaneous panniculitis-like T-cell lymphoma (SPTCL) in 11.1%, anaplastic large cell lymphoma (ALCL) in 4.4%, which were ALK^+ in 1 of 6), ALK^- in 3 of 6, and unknown ALK status in 2 of 6, primary cutaneous anaplastic large cell lymphoma (C-ALCL) in 0.7%, and enteropathy-associated T-cell lymphoma (EATL) in 0.7%.

CD30 expression

Overall, the expression of CD30 in PTCLs was 34.8% (47/135). The expression of CD30 was significantly associated with histological subtypes ($p<0.001$). There was a higher prevalence in ALCL/C-ALCL (100.0%), nasal NKTCL (79.2%), and PTCL-NOS (30.6%). The expression of CD30 in PTCL subtypes are summarized in Table 1.

Clinical features and treatment outcomes

The median age was 52 years (ranged, 16 to 89 years) and the male-to-female ratio was 2.64:1. Most patients were under 60 years of age (65.9%), good ECOG scores (85.9%), low prognostic scores [IPI score 0 to 2 (76.1%), PIT score 0 to 1 (61.2%), and ITPCLP score 0 to 1 (91.8%)], and presented with extranodal lesions (84.4%). Fifty-seven percent of the patients had low Ann Arbor stage. B symptoms presented in 51.1%, elevated LDH in 59.7%, and BM involvement in 22.7% of the patients.

One hundred thirteen patients were treated with chemotherapy. Of those, anthracycline-based chemotherapy (CHOP, CHOP-like, EPOCH, and hyper-CVAD regimen) was used in 98 patients (86.7%). Eighteen percent of the 134 patients were treated with radiotherapy. One hundred four patients (77.6%) were included in the response estimation. The overall response rate was 70.2% with a complete response rate of 51.9%. The clinical features and treatment outcomes of 135 patients are summarized in Table 2.

Table 1. CD30 immunohistochemical expression in peripheral T-cell lymphoma subtypes ($p<0.001$)

Cell type	Patients; n	CD30 positivity; n (%)
All PTCLs	135	47 (34.8)
PTCL-NOS	49	15 (30.6)
Nasal NKTCL	24	19 (79.2)
AITL	21	4 (19.0)
CTCL	18	2 (11.1)
SPTCL	15	0 (0.0)
ALCL/C-ALCL	7	7 (100)
EATL	1	0 (0.0)

PTCLs=peripheral T-cell lymphomas; PTCL=peripheral T-cell lymphoma; NOS=not otherwise specified; AITL=angioimmunoblastic T-cell lymphoma; Nasal NKTCL=extranodal NK/T-cell lymphoma, nasal type; SPTCL=subcutaneous panniculitis-like T-cell lymphoma; CTCL=cutaneous T-cell lymphoma; ALCL=anaplastic large cell lymphoma; C-ALCL=primary cutaneous anaplastic large cell lymphoma; EATL=enteropathy-associated T-cell lymphoma

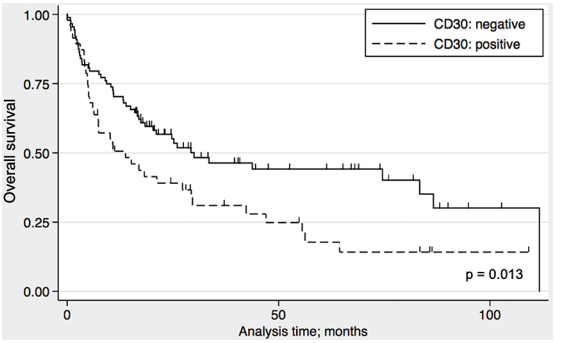

Figure 2. Survival of PTCL patients according to CD30 expression.

Survival outcomes

The survival analysis was performed on 135 patients. The median follow-up duration was 18 months. Eighty-four patients (62.2%) died in the present study. The median survival was 25 months with a projected 5-year survival of 37.0%.

With univariate analysis, CD30 positivity was significantly associated with poor survival outcome ($CD30^-$ 30 months versus $CD30^+$ 14 months, $p=0.013$) (Figure 2). Moreover, advanced age, poor ECOG scores, extranodal lesion greater than 1, B symptoms, advanced stage, high LDH level, platelet of less than 150,000 per μL, BM involvement, PTCL subtypes,

Table 2. The clinical data and treatment outcomes of peripheral T-cell lymphoma patients

Variables	No. of patients; n (%)	Variables	No. of patients; n (%)
Sex: male/female	98/37 (72.6/27.4)	IPI	
Age (years); median (range)	52 (16-89)	L-LI	102 (76.1)
≤60	89 (65.9)	HI-H	32 (23.9)
>60	46 (34.1)	PIT	
PS		Score 0 to 1	82 (61.2)
ECOG 0 to 1	116 (85.9)	Score 2 to 4	52 (38.8)
ECOG 2 to 4	19 (14.1)	IPTCLP	
Histology		Score 0 to 1	123 (91.8)
PTCL-NOS	49 (36.3)	Score 2 to 3	11 (8.2)
AITL	21 (15.6)	Treatment	
Nasal NKTCL	24 (17.8)	None	22 (16.3)
SPTCL	15 (11.1)	Anthracycline-based	98/113 (86.7)
CTCL	18 (13.3)	Others	15/113 (13.3)
ALCL	6 (4.4)	Radiotherapy	
C-ALCL	1 (0.7)	None	110 (82.1)
EATL	1 (0.7)	Yes	24 (17.9)
Stage		Response	
I-II	77 (57.0)	ORR	73 (70.2)
III-IV	58 (43.0)	CR	54 (51.9)
Extranodal		PR	19 (18.3)
No	21 (15.6)	SD	4 (3.8)
Yes	114 (84.4)	PD	27 (26.0)
Extranodal >1	27 (23.7)	Salvage	
B symptoms	69 (51.1)	No	90 (67.7)
BM involvement	30 (22.7)	Yes	43 (32.3)
LDH IU/L; median (range)	650 (155 to 2,735)	Death	
> normal	80 (59.7)	No	51 (37.8)
Platelet <150,000	12 (8.9)	Yes	84 (62.2)

PS=performance status, BM=bone marrow, ECOG=Eastern Cooperative Oncology Group, PTCL=peripheral T-cell lymphoma, NOS=not otherwise specified, AITL=angioimmunoblastic T-cell lymphoma, Nasal NKTCL=extranodal NK/T-cell lymphoma, nasal type, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, CTCL=cutaneous T-cell lymphoma, ALCL=anaplastic large cell lymphoma, C-ALCL=primary cutaneous 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, IPTCLP=International T-cell Lymphoma Project score, ORR=overall response rate, CR=complete remission, PR=partial response, SD=stable disease, PD=progressive disease

and poor prognostic scores demonstrated prognostic significance on survival. Among all PTCL subtypes, CTCL and SPTCL had better outcomes (median OS, not reached and 84.6 months, respectively). From Cox regression analysis, only PTCL subtypes remained independent prognostic predictor for survival in the present study. The univariate and multivariate analysis of factors influencing OS of PTCL is shown in Table 3.

Discussion

PTCLs are more prevalent in the Asian populations that predominantly affect adult males. Most of the patients presented with advanced stage and had a poor survival outcome. In recent years, several biomarkers in PTCLs have been studied to identify their role in PTCL genesis and to develop a targeted immunotherapy for these tumors.

CD30 expression was initially described in Hodgkin lymphoma (HL) and ALCL. Furthermore, previous studies reported variable numbers of CD30 expression in other PTCL subtypes[6-12,17]. Several therapeutic agents were also developed to target CD30, which produced variable clinical outcomes.

Table 3. Univariate and multivariate analysis of factors influencing overall survival of PTCL

Parameters	Univariate analysis (Log-rank test)	Multivariate analysis	
	p-value	Hazard ratio (95% confidence interval)	p-value
CD30 positive	0.013	1.24 (0.73 to 2.10)	0.430
Advanced age	0.040	1.07 (0.51 to 2.26)	0.858
Poor ECOG scores	0.001	1.99 (0.78 to 5.08)	0.150
PTCL subtypes	<0.001	0.75 (0.62 to 0.92)	0.005
Extranodal lesion >1	0.001	1.31 (0.34 to 5.04)	0.695
B symptoms	<0.001	1.24 (0.57 to 2.70)	0.587
Advanced stage	<0.001	0.87 (0.37 to 2.06)	0.748
High LDH level	0.012	1.25 (0.49 to 3.17)	0.637
Platelet <150,000/μL	<0.001	0.43 (0.17 to 1.07)	0.069
BM involvement	<0.001	0.63 (0.21 to 1.93)	0.423
IPI HI-H	<0.001	1.26 (0.31 to 5.15)	0.743
PIT score 2 to 4	<0.001	2.50 (0.88 to 7.12)	0.086
IPTCLP score 2 to 3	0.015	0.58 (0.14 to 2.45)	0.459

ECOG=Eastern Cooperative Oncology Group; PTCL=peripheral T-cell lymphoma; LDH=lactate dehydrogenase, BM=bone marrow; IPI=International Prognostic Index; L-LI=low to low-intermediate; HI-H=high-intermediate to high; PIT=prognostic index for T-cell lymphoma; IPTCLP=International T-cell Lymphoma Project score

A landmark study by Younes et al reported that antibody-drug conjugate brentuximab vedotin (SGN-35) induced durable responses in tumor progression in patients with relapsed CD30-positive lymphomas[18]. Based on these promising results, brentuximab vedotin was approved by the US Food and Drug Administration for use in relapsed HL and ALCL in 2011[25]. Recently, brentuximab vedotin has been used in combination with cyclophosphamide, doxorubicin, and prednisolone (A+CHP) to compare with CHOP regimen for previously untreated $CD30^+$ PTCLs in phase 3 clinical trial. The front-line treatment with A+CHP exhibited significant improvement in progression-free survival and OS with manageable side effects[21]. Therefore, the present study was designed to assess the prevalence of CD30 expression and their relation to survival in PTCLs. Ultimately, the results will benefit a feasibility assessment of antiCD30 antibodies in PTCL treatment.

The present study submitted the cases of 135 patients between 2001 and 2012 with a diagnosis of PTCL according to WHO classification 2008. The common PTCL subtypes in the present study were PTCL-NOS, nasal NKTCL, and AITL. Most of the patients were middle-aged male, good ECOG scores, low prognostic scores, and presented with extranodal lesions. Most patients were treated with anthracycline-based chemotherapy, which produced favorable response outcomes.

CD30 positivity was demonstrated in one-third of the patients. The expression of CD30 was significantly different among the PTCL subtypes. It was more expressed in ALCL/C-ALCL, nasal NKTCL, and PTCL-NOS. Although the patients had a favorable response from front-line chemotherapy, the median OS was a disappointing outcome. With a median follow-up time of 18 months, the median OS was 25 months with a projected 5-year survival of 37.0%. Moreover, CD30 positivity demonstrated an inferior outcome in PTCLs ($CD30^-$ 30 months vs. $CD30^+$ 14 months, p=0.013). From these results, the antiCD30 antibodies might have a potential role in PTCL treatment, especially in ALCL, nasal NKTCL, and PTCL-NOS.

To date, there are limited data in the prevalence of CD30 expression in PTCLs and the results are discordant. The prevalence of CD30 expression in the present study was similar to the report by Sabattini et al[17]. They assessed CD30 expression in 192 PTCLs other than ALCL. They found positivity in 43.2% with a higher prevalence in EATL type 1, transformed mycosis fungoides, nasal NKTCL, and PTCL-NOS. Nevertheless, they did not assess the association of CD30 expression with survival outcome[17]. Another study from Bisig et al explored the molecular relationship between $CD30^+$ and $CD30^-$ PTCL-NOS and the clinical outcomes in 36 cases. Their results revealed that $CD30^-$ PTCL-NOS tended to have an inferior outcome[26].

The discordant results were possibly caused from

a small number of patients and a different proportion of PTCL subtypes in each study. Moreover, the standard cutoffs for CD30 positivity were not well established. In addition, the heterogeneity of treatment options and the less accessibility of autologous stem cell transplantation might contribute to the poor survival outcomes in the present study cohort. Therefore, large number of patients, subtype analyses, and standard cutoffs for CD30 positivity should be further investigated for more accurate data.

Even though the present study enrolled the data of the years before the revision of WHO classification 2016, the major diagnostic criteria, the prevalence of CD30 expression, and treatment strategies of PTCLs have not changed much recently. Therefore, the present study data could represent the inferior outcome of $CD30^+$ PTCLs and the potential role of conjugated antiCD30 antibodies in those patients.

Conclusion

CD30 positivity in PTCLs was demonstrated in one-third of patients and statistically associated with PTCL subtypes. There was more frequent expression in ALCL, nasal NKTCL, and PTCL-NOS. From survival analysis, the CD30 positivity subgroup showed significantly inferior outcomes.

What is already known on this topic?

CD30 variably expresses on several non-Hodgkin lymphomas, including PTCLs. Recently, the use of antiCD30 monoclonal antibodies in front-line and relapsed or refractory PTCL treatment unveiled promising outcomes. Nevertheless, the prevalence data of CD30 expression in PTCLs is scarce and discordant among studies.

What this study adds?

CD30 positivity was identified in one-third of PTCL patients especially in ALCL, nasal NKTCL, and PTCL-NOS subtypes. Moreover, $CD30^+$ PTCL patients demonstrated an inferior survival outcome to $CD30^-$ PTCL patients. This finding highlighted the potential role of anti CD30 monoclonal antibodies in PTCL treatment.

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Authors' contributions

Julamanee J and Lekhakula A designed the study, analyzed the data, wrote, and edited the manuscript. Kayasut K reviewed and assessed all tissue specimens and edited the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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