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Profiles of serum cytokines and their clinical implications in patients with peripheral T-cell lymphoma

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ABSTRACT

To better predict the outcomes of patients with peripheral T-cell lymphoma (PTCL), we measured the levels of various cytokines in serum samples from patients with PTCL and analyzed their clinical outcomes. We measured 34 cytokines in samples from 121 PTCL patients (55 PTCL-not otherwise specified (NOS), 44 angioimmunoblastic T-cell lymphoma (AITL), and 22 ALK$^-$ anaplastic large cell lymphoma) at diagnosis. Their impact on clinical outcomes, including overall survival and complete response rate, were analyzed with other clinical variables. The median age of patients was 58 years (range, 20–85 years) and 81 patients (66.9%) were male. The median overall survival among all patients was 56.1 months (95% CI 21.4–90.8) and median progression-free survival was 19.3 months (95% CI 12.3–26.3). Patients with AITL were more likely to express higher levels of serum cytokines, and 7 cytokines showed mean levels that were significantly higher than those in other subtypes. In this subgroup, IL-10 higher than 3.8 pg/mL was associated with adverse outcomes. In patients with ALK$^-$ anaplastic large cell lymphoma, 9 cytokines showed a prognostic impact, with higher levels of interferon γ, interleukin (IL)-8, IL-10, IL-17, IL-23, IP-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1β, and RANTES negatively affecting clinical outcomes. In PTCL-NOS, patients with elevated levels of interferon γ, IL-7, and IL-23 showed poor outcomes. The current analysis demonstrated different cytokine profiles according to histologic subtype, which revealed the heterogeneity of PTCL. In addition, cytokine levels can be used as prognostic markers and may be useful for therapeutic applications in PTCL patients.

1. Introduction

Peripheral T-cell lymphoma (PTCL) represents a group of malignant lymphoproliferative diseases that arise from post-thymic T-lymphocytes and accounts for approximately 10% of all non-Hodgkin's lymphoma cases worldwide. Because of its rarity and heterogeneity, few studies have examined the biologic features and clinical outcomes of the disease. The molecular understanding of PTCL has remarkably advanced, particularly the role of the tumor microenvironment. For instance, angioimmunoblastic T-cell lymphoma (AITL) derived from T-follicular helper cells was found to involve various cellular interactions with the tumor microenvironment by expressing high levels of CXCL13 [1], and patients with this subtype demonstrated improved clinical outcomes following treatment with immunomodulatory agents [2,3]. Several *in vivo* and *in vitro* studies showed that the growth and survival of malignant T-cells depend on alternatively activated (M2) macrophages in the microenvironment [4,5], which may be enhanced by various cytokines such as interleukin (IL)-4, IL-13, and IL-10 [6]. The T-cell transcription factor GATA-binding protein 3 (GATA-3) is involved in the expression of these cytokines [7], and a recent study of a subset of patients with PTCL-not otherwise specified (NOS) showing GATA-3 expression were more likely to have a poor prognosis [8,9]. Moreover, aberrations in the JAK/STAT pathway were found to be involved in IL-10-mediated lymphomagenesis by M2 macrophages [8,10]. Thus, the tumor microenvironment contributes to the survival, progression, and immune evasion of malignant lymphocytes through various pathways.

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Table 1
Demographics and clinical outcomes of the patients.

Characteristics	N (%)				
	AITL (N = 44)	ALCL, ALK$^-$ (N = 22)	PTCL-NOL (N = 55)	Total (N = 121)	P
Median age (range)	61 (30–85)	51 (21–79)	60 (20–85)	58 (20–85)	0.221
≤60 years	22 (50.0)	16 (72.7)	31 (56.4)	69 (57.0)	
> 60 years	22 (50.0)	6 (27.3)	24 (43.6)	52 (43.0)	
Sex					0.459
Male	27 (61.4)	14 (63.6)	40 (72.7)	81 (66.9)	
Female	17 (38.6)	8 (36.4)	15 (27.3)	40 (33.1)	
Performance status*					0.240
0–1	36 (81.8)	21 (95.5)	44 (80.0)	101 (83.5)	
2–3	8 (18.2)	1 (4.5)	11 (20.0)	20 (16.5)	
Ann Arbor Stage					0.023
I–II	5 (11.4)	9 (40.9)	14 (25.5)	28 (23.1)	
III–IV	39 (88.6)	13 (59.1)	41 (74.5)	93 (76.9)	
Extranodal site(s)					0.567
0–1	24 (54.5)	15 (68.2)	32 (58.2)	71 (58.7)	
More than 2	20 (45.5)	7 (31.8)	23 (41.8)	50 (41.3)	
Serum LDH**					0.121
Within normal limit	13 (29.5)	12 (54.5)	24 (43.6)	49 (40.5)	
Increased	31 (70.5)	10 (45.5)	31 (56.4)	72 (59.5)	
IPI† risk group					0.083
Low	9 (20.4)	12 (54.6)	14 (25.5)	35 (28.9)	
Low-intermediate	8 (18.2)	4 (18.2)	13 (23.6)	25 (20.7)	
High-intermediate	14 (31.8)	3 (13.6)	18 (32.7)	35 (28.9)	
High	13 (29.6)	3 (13.6)	10 (18.2)	20 (21.5)	
B symptom(s)					0.413
Absent	25 (56.8)	15 (68.2)	38 (69.1)	78 (64.5)	
Present	19 (43.2)	7 (31.8)	17 (30.9)	43 (35.5)	
Bone marrow involvement					0.806
Absent	33 (75.0)	16 (72.7)	38 (69.1)	87 (71.9)	
Present	11 (25.0)	6 (27.3)	17 (30.9)	34 (28.1)	
ALC†† (median, range)	1038 (44–3462)	1516 (800–3989)	1171 (0–6501)	1152 (0–6501)	0.015
≤600/μL	11 (25.0)	0 (0.0)	6 (10.9)	17 (14.0)	
> 600/μL	33 (75.0)	22 (100.0)	49 (89.1)	104 (86.0)	
Serum albumin					0.061
≤3.3 g/dL	17 (38.6)	5 (22.7)	14 (25.5)	39 (32.2)	
> 3.3 g/dL	27 (61.4)	17 (77.3)	41 (74.5)	82 (67.8)	
Front-line regimen‡					0.709
CHOP-based	42 (95.4)	20 (91.0)	52 (94.6)	114 (94.2)	
ICE/Dexa	1 (2.3)	1 (4.5)	2 (3.6)	4 (3.3)	
Others	1 (2.3)	1 (4.5)	1 (1.8)	3 (2.5)	
Clinical outcomes					
Overall survival (months, median, 95% confidence interval (CI))	70.3 (37.3–103.3)	Not estimable	22.1 (13.4–30.8)	56.1 (21.4–90.8)	0.119
Progression-free survival (median, 95% CI)	66.3 (0–133.2)	23.2 (Not estimable)	11.7 (9.0–14.4)	19.3 (12.3–26.3)	0.039
Tumor response					0.106
Complete response (CR)	31 (70.5)	15 (68.2)	28 (50.9)	74 (61.2)	
Non-CR	13 (29.5)	7 (31.8)	27 (49.1)	47 (38.8)	

* by Eastern Cooperative Oncology group scale.
** Lactate dehydrogenase.
† International prognostic index.
†† Absolute lymphocyte count; PTCL-NOS, peripheral T-cell lymphoma, not-otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL, ALK$^-$ anaplastic large cell lymphoma.
‡ CHOP, cyclophosphamide, doxorubicine, vincristine, prednisone; ICE, ifosfamide, carboplatin, etoposide.

Cytokines are major non-cellular components in the tumor microenvironment and act as messengers between malignant cells and cellular components of the tumor microenvironment [11]. The roles of cytokines in Hodgkin's lymphomas or B-cell non-Hodgkin lymphomas have been widely investigated. However, little is known about that of PTCL. We recently found that in 37 patients with AITL, elevated serum IL-10 and infiltration of alternatively activated macrophages were associated with poor survival [12]. Using an expanded cohort and cytokine analysis, we further evaluated how the pre-treatment serum level of various cytokines impact clinical outcomes in patients with PTCL.

2. Material and methods

2.1. Patients

Patients in our prospective cohort studies (NCT#00822731 and NCT#01877109) who met the following criteria were included in the present study. (1) Patients with newly diagnosed a mature T-cell

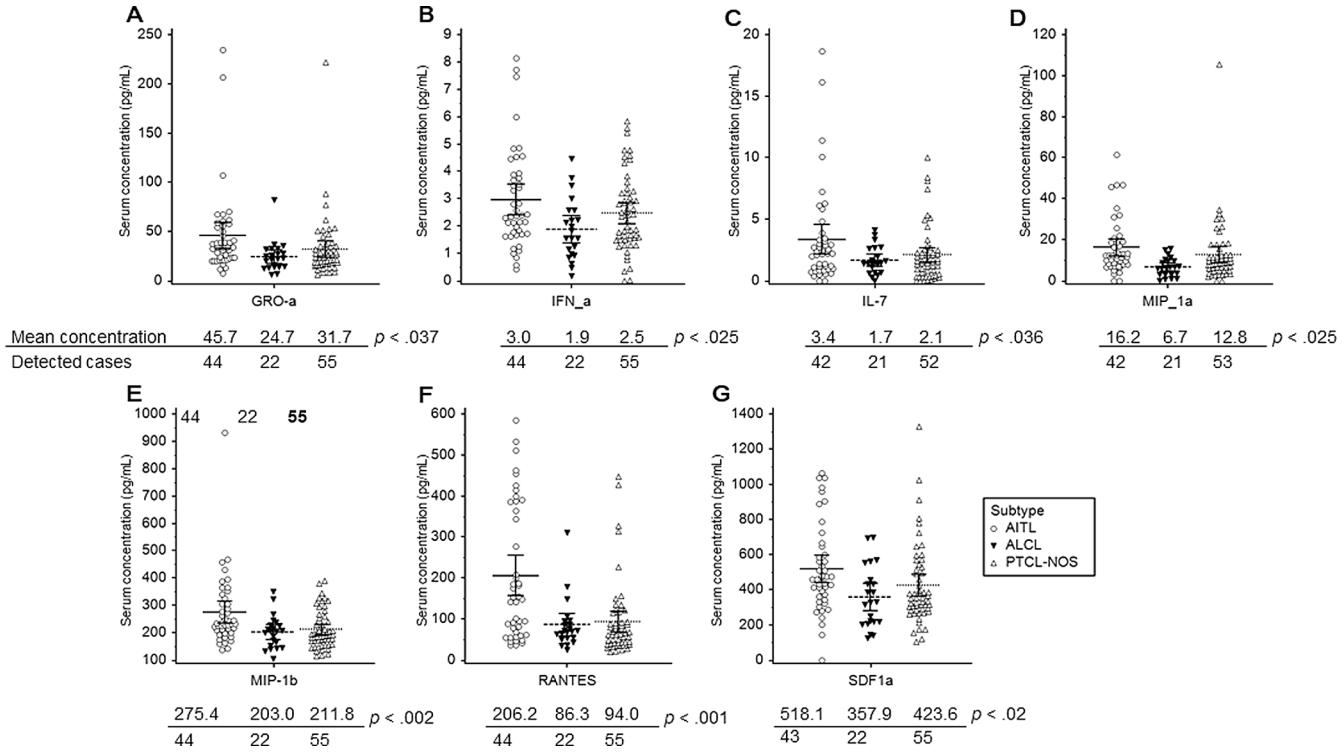

Fig. 1. Seven cytokines that patients with AITL showed significantly higher mean levels compared to patients with other histology. They were measured through multiplex chemokine assay. A, GROα; B, IFN-α; C, IL-7; D, MIP-1α; E, MIP-1β; F, RANTES; and G, SDF1α. Numbers under the X-axis indicates mean levels of each cytokines (pg/mL), and number of detected cases. The mean levels were compared using the one-way analysis of variance method.

Table 2
Clinical outcomes of patients with AITL.

	N (%)	Overall survival (median, 95% CI)	*P*	CR (*N*, rate%)	*P*
IL-10			0.005		0.009
≤3.8 pg/mL	20 (45.5)	Not reached		18 (90.0)	
> 3.8 pg/mL	24 (54.5)	29.4 (0.0–65.0)		13 (54.2)	
Age			0.893		0.322
≤60 years	22 (50.0)	70.3 (0.0–142.7)		17 (77.3)	
> 60 years	22 (50.0)	83.9 (Not estimable)		14 (63.6)	
ECOG PS			0.005		0.024
0–1	36 (81.8)	80.9 (37.4–124.4)		28 (77.8)	
2–3	8 (18.2)	2.4 (1.6–3.2)		3 (37.5)	
Ann Arbor stage			0.175		0.124
1–2	5 (11.4)	Not reached		5 (100.0)	
3–4	39 (88.6)	70.3 (35.8–104.8)		24 (66.7)	
Extranodal site(s)			0.200		0.469
0 ~ 1	24 (54.5)	80.9 (65.2–96.6)		18 (75.0)	
More than 2	20 (45.5)	33.3 (Not estimable)		13 (65.0)	
Serum LDH			0.340		0.040
Within normal limit	13 (29.5)	80.9 (Not estimable)		12 (92.3)	
Increased	31 (70.5)	70.3 (0.0–142.1)		19 (61.3)	
ALC			0.002		0.036
≤600/μL	11 (25.0)	14.6 (1.4–27.8)		5 (45.5)	
> 600/μL	33 (75.0)	50.9 (65.2–96.6)		26 (78.8)	
Serum albumin			0.039		0.043
≤3.3 g/dL	17 (38.6)	29.4 (0.0–69.7)		9 (52.9)	
> 3.3 g/dL	27 (61.4)	70.3 (17.7–122.9)		8 (81.5)	

Multivariate analysis for overall survival

	Hazard ratio	95% CI	*P*
ECOG 2–3	10.216	1.918–54.427	0.006
ALC ≤ 600/μL	5.208	1.432–19.463	0.012
Albumin ≤ 3.3 g/dL	2.316	0.458–11.703	0.310
IL-10 > 3.8 pg/mL	8.747	1.703–44.919	0.009

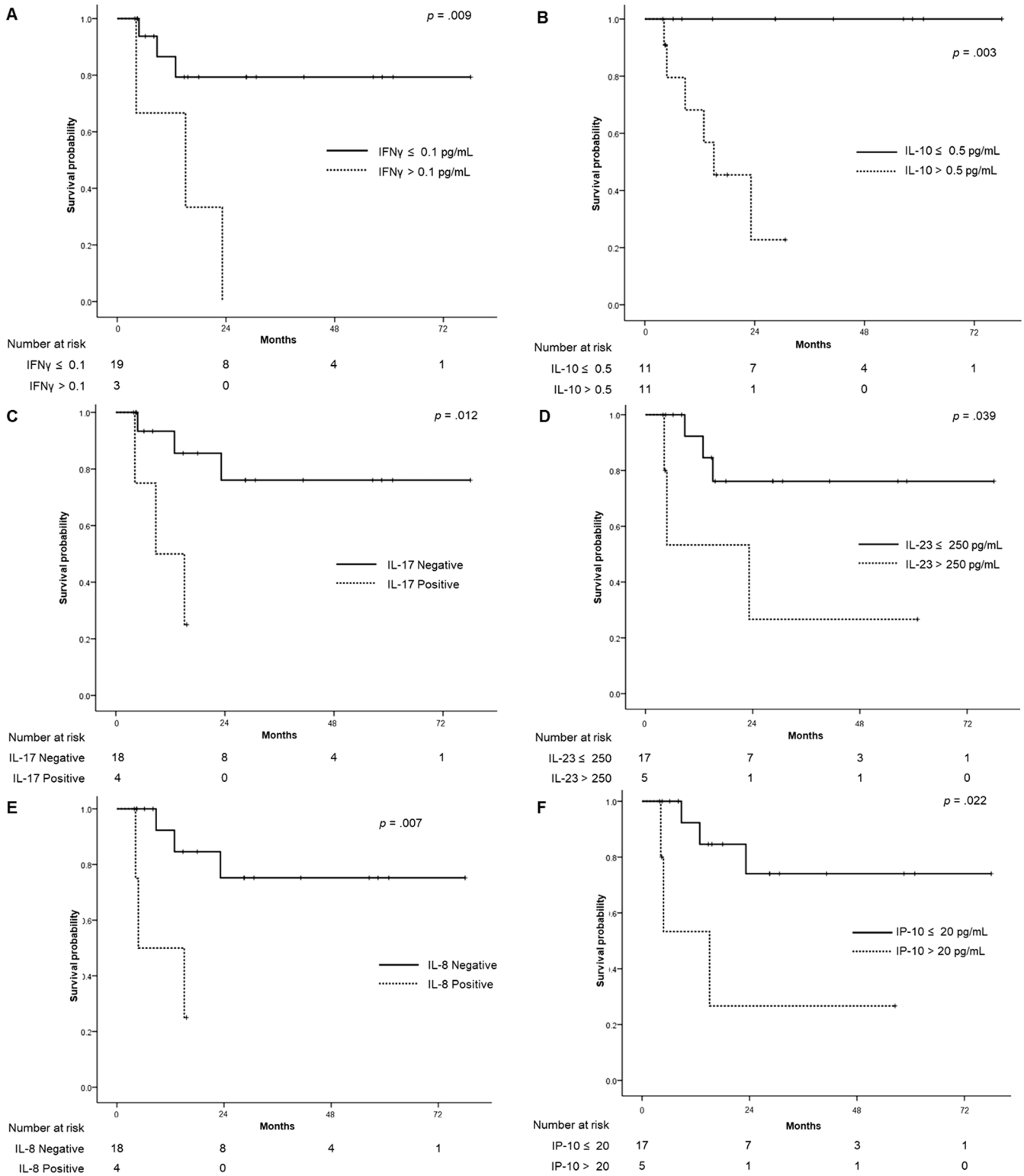

Fig. 2. Kaplan-Meier curves for overall survival of patients with ALCL according to the level of cytokines (N = 22). They were measured through multiplex chemokine assay. A, IFN-γ; B, IL-10; C, IL-17; D, IL-23; E, IL-8; F, IP-10; G, MCP-1; H, MIP-1β; and I, RANTES. Log-rank test was used to compare the overall survival.

neoplasm according to the 2008 World Health Organization classification [13]; AITL, ALK$^-$-anaplastic large-cell lymphoma (ALCL), or PTCL-NOS, and (2) Patients whose serum samples were collected for measurement of cytokines before administration of any treatments after receiving written informed consent. This study was approved by the Institutional Review Board of Samsung Medical Center. Clinical data of patients including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, Ann-Arbor stage, serum lactate dehydrogenase (LDH) level, number of extranodal involvements, bone marrow involvement, B symptoms, absolute lymphocyte counts (ALC), serum albumin concentration, front-line treatment regimens, tumor response, date of progression, and date of death were collected during the prospective cohort studies. For survival analysis, we updated the survival status in October 2016.

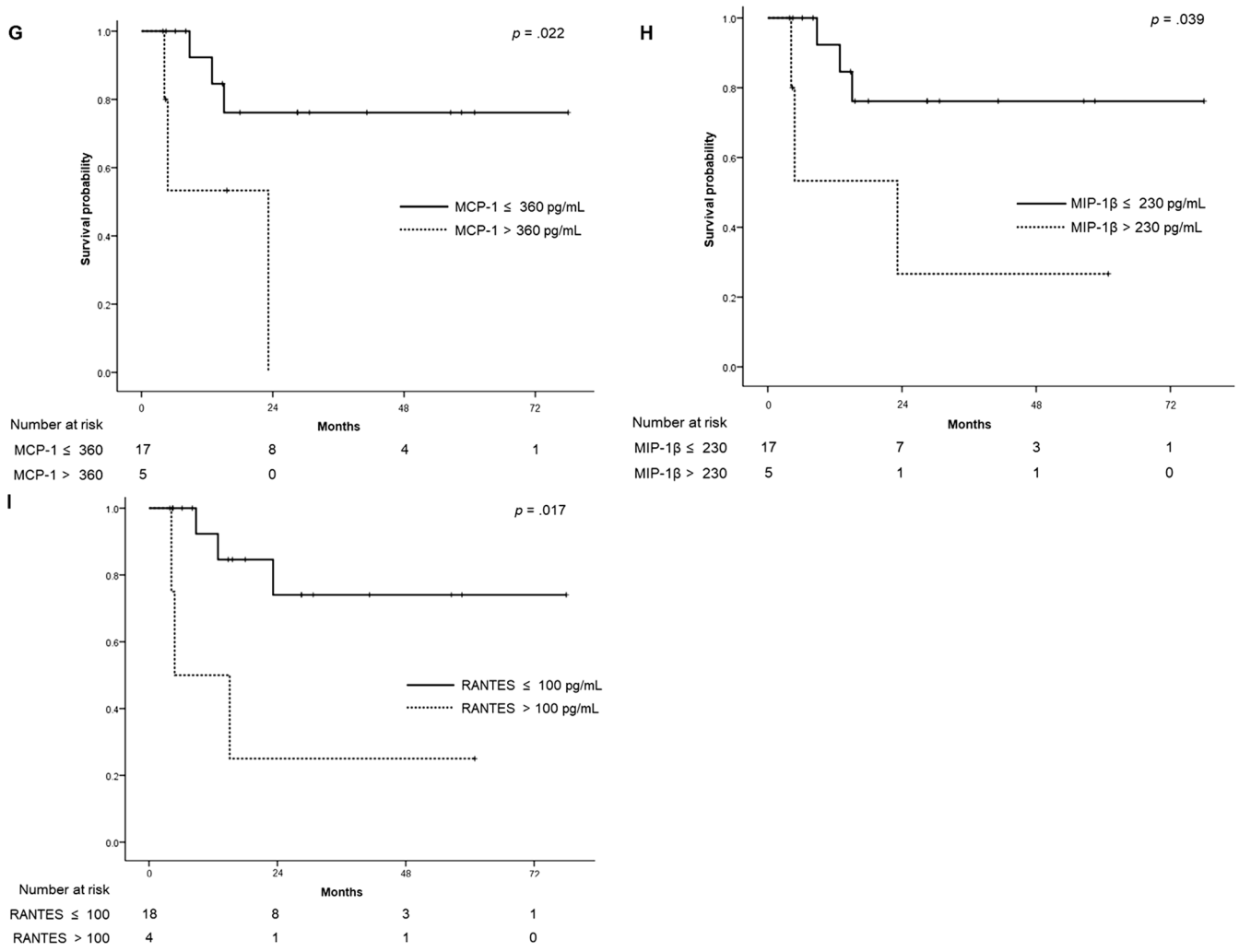

Fig. 2. (*continued*)

2.2. Multiplex cytokine assay

Serum samples were collected at diagnosis and stored at −80 °C until analysis. Serum aliquots had not been previously thawed before use in the multiplex chemokine assay. We measured the levels of eotaxin-1, GROα, interferon (IFN)-α, IFN-γ, IL-1α, IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17α, IL-18, IL-21, IL-22, IL-23, IL-27, IL-31, interferon γ-induced protein (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), MIP-1β, regulated on activation, T cell expressed and secreted (RANTES), stromal cell-derived factor 1α (SDF1α), tumor necrosis factor (TNF)-α, and TNF-β in triplicate with the Procarta cytokine profiling kit (Panomics, Fremont, CA, USA) using the Bio-Plex Cytokine Assay System (Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions. To estimate the reference ranges of cytokines, we measured the levels of serum cytokines in 11 normal individuals (4 males and 7 females, median age 42 (range 29–72)).

2.3. Statistical analysis

The primary end-point was overall survival (OS), measured from the date of diagnosis to the date of death or last follow-up. The secondary end-points were progression-free survival (PFS), measured from the date of diagnosis to the date of progressive disease, death, or last follow-up, and complete response (CR) rate, which was assessed after the 3rd and 6th cycles of chemotherapy by performing computed tomography (CT) and positron emission tomography (PET)/CT scans following the revised response criteria for malignant lymphoma [14]. Optimal cutoff values for cytokines were determined by one of the following if the value could discriminate clinical outcomes: (1) receiver-operating characteristic curve methods; (2) 25th, 50th, or 75th percentile values; (3) negative vs. positive detection. Additionally, clinical parameters were analyzed for survival outcomes and tumor response. All survival parameters were calculated using the Kaplan-Meier method and compared using a log-rank test. Tumor responses were compared using Pearson's λ^2 test, and the mean levels of serum cytokines by histologic subtypes were compared by one-way analysis of variance. To analyze whether the distributions of value of cytokines were identical or different between the normal individuals and the PTCL patients, an independent-sample Kruskal-Wallis test was carried out. In all comparisons, *P*-values less than 0.05 were considered statistically significant, and all *P*-values corresponded to two-sided significance tests. Statistical analyses were carried out using SPSS software version 17.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

Between September 2008 and December 2014, a total of 121 patients were eligible for analysis. The median age was 58 years (range, 20–85 years) and 81 patients (66.9%) were male. Ninety-three patients (76.9%) had advanced disease at the time of diagnosis with stage III–IV

Table 3
Clinical outcomes of patients with ALCL.

	N (%)	Overall survival (median, 95% CI)	*P*	CR (*N*, rate%)	*P*
IFN-γ			0.009		0.006
≤0.1 pg/mL	19 (86.4)	Not reached		15 (78.9)	
> 0.1 pg/mL	3 (13.6)	15.1 (0.0–32.5)		0 (0.0)	
IL-8			0.007		0.040
Negative	18 (81.8)	Not reached		14 (77.8)	
Positive	4 (18.2)	4.8 (0.0–15.5)		1 (25.0)	
IL-10			0.003		0.170
≤0.5 pg/mL	11 (50.0)	Not reached		9 (81.8)	
> 0.5 pg/mL	11 (50.0)	15.1 (5.2–25.0)		6 (54.5)	
IL-17			0.012		0.388
Negative	18 (81.8)	Not reached		13 (72.2)	
Positive	4 (18.2)	8.8 (0.0–19.5)		2 (50.0)	
IL-23			0.039		0.124
≤250 pg/mL	17 (77.3)	Not reached		13 (76.5)	
> 250 pg/mL	5 (22.7)	8.0 (7.4–39.0)		2 (40.0)	
IP-10			0.022		0.124
≤20 pg/mL	17 (77.3)	Not reached		13 (76.5)	
> 20 pg/mL	5 (22.7)	15.1 (6.1–24.1)		2 (40.0)	
MCP-1			0.022		0.124
≤360 pg/mL	17 (77.3)	Not reached		13 (76.5)	
> 360 pg/mL	5 (22.7)	23.2 (Not estimable)		2 (40.0)	
MIP-1β			0.039		0.124
≤230 pg/mL	17 (77.3)	Not reached		13 (76.5)	
> 230 pg/mL	5 (22.7)	23.2 (7.4–39.0)		2 (40.0)	
RANTES			0.017		0.040
≤100 pg/mL	18 (81.8)	Not reached		14 (77.8)	
> 100 pg/mL	4 (18.2)	4.8 (0.0–15.5)		1 (25.0)	
Age			0.064		0.032
≤60 years	16 (72.7)	Not reached		13 (81.3)	
> 60 years	6 (27.3)	23.2 (Not estimable)		2 (33.3)	
ECOG PS			< 0.001		0.134
0–1	21 (95.5)	Not reached		15 (71.4)	
2–3	1 (4.5)	4.2 (Not estimable)		0 (0.0)	
Ann Arbor stage			0.058		0.421
1–2	9 (40.9)	Not reached		7 (77.8)	
3–4	13 (59.1)	23.2 (Not estimable)		8 (61.5)	
Extranodal site(s)			0.402		0.448
0–1	15 (68.2)	Not reached		11 (73.3)	
More than 2	7 (31.8)	Not reached		4 (57.1)	
Serum LDH			0.076		0.010
Within normal limit	12 (54.5)	Not reached		11 (91.7)	
Increased	10 (45.5)	23.2 (Not estimable)		4 (40.0)	
ALC	All cases were > 600/μL				
Serum albumin			0.003		0.0040
≤3.3 g/dL	5 (22.7)	4.8 (Not estimable)		1 (25.0)	
> 3.3 g/dL	17 (77.3)	Not reached		14 (77.8)	

disease. Most patients ($N = 114$, 94.2%) had been administered CHOP-based therapy. PTCL-NOS was the most frequent type ($N = 55$, 45.5%) followed by AITL ($N = 44$, 36.4%) and ALK$^-$ ALCL ($N = 22$, 18.1%). Compared to the other subtypes, patients with AITL more frequently had advanced stage disease ($P = 0.023$), lymphopenia ($P = 0.015$), and hypoalbuminemia ($P = 0.061$). Other details are shown in Table 1.

3.2. Clinical outcomes

The median OS was 56.1 months (95% confidence interval (CI) 21.4–90.8) and median PFS was 19.3 months (95% CI 12.3–26.3). Survival of patients with PTCL-NOS was least favorable, although OS was not significantly different compared to the other groups (Supplementary Fig. S1). The CR rate was 61.2% (74/121). Patients with PTCL-NOS showed the lowest CR (50.9%), but the difference was not significant (Table 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cyto.2018.10.009.

3.3. Profiles of serum cytokine in 3 major subtypes

Next, we analyzed the profiles of serum cytokines (Supplementary Table 1). Of the 34 cytokines assessed, 8 (Eotaxin-1, GROα, IFN-α, IL-1α, IP-10, MCP-1, MIP-1β, RANTES, and TNFα) were detected in the whole population. For the 11 cytokines expressed only in a small number of patients (GM-CSF, IL-1β, IL-2, IL-4, IL-5, IL-9, IL-13, IL-21, IL-27, IL-31, and TNFβ), their profiles and clinical outcomes were not analyzed. In the normal individuals, 11 cytokines, that is, eotaxin-1, GROα, IFN-α, IL-1α, IL-23, IP-10, MCP-1, MIP-1β, RANTES, SDF1α, and TNFα were detected in the whole population, while 20 cytokines, that is, GM-CSF, IFN-γ, IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-15, IL-17α, IL-18, IL-21, IL-22, IL-27, IL-31, and TNFβ were expressed only in a small number of cases. When we compared the median values and range between the normal individuals and PTCL patients, those of all cytokines except eotaxin-1 were significantly different (Supplementary Table 1).

Patients with AITL were more likely to express cytokines. Among the total available cases (No. of patients × 34 cytokines), 829 patient-case with AITL (55.4%), 352 patient-case with ALK$^-$ ALCL (47.1%), and 939 patient-case with PTCL-NOS (50.2%) expressed cytokines ($P < 0.001$). Additionally, 7 cytokines showed mean levels that were significantly higher in AITL than those in other subtypes, reflecting the inflammatory milieu of the disease (Fig. 1). Notably, several cytokines involved in T-follicular helper cell pathways such as IL-4, IL-6, IL-10, and IL-21 were frequently expressed in this disease.

3.4. Serum cytokines and their association with outcomes of AITL

As observed previously [12], higher expression of IL-10 was associated with poor clinical outcomes. The median OS for 24 patients (54.5%) with IL-10 expression higher than 3.8 pg/mL was 29.4 months (95% CI 0.0–65.0) which was significantly shorter than that of other patients ($P = 0.005$) (Supplementary Fig. S2). The CR rate was also lower for these patients (54.2% vs. 90.0%, $P = 0.009$). Several clinical parameters including ECOG performance scale, ALC, and serum albumin level were also associated with clinical outcomes. In multivariate analysis of OS, elevation of IL-10 (hazard ratio (HR) 8.747, 95% CI 1.703–44.919, $P = 0.009$) along with an ECOG performance scale of 2–3 (HR 10.216, 95% CI 1.918–54.427, $P = 0.006$), and ALC ≤ 600/μL (HR 5.208, 95% CI 1.432–19.463, $P = 0.012$) were associated with low OS (Table 2).

3.5. Serum cytokines and their association of outcomes in ALK- ALCL

A total of 9 cytokines were correlated with prognosis in patients with ALK-negative ALCL. Higher expression of IFN-γ (> 0.1 pg/mL), IL-

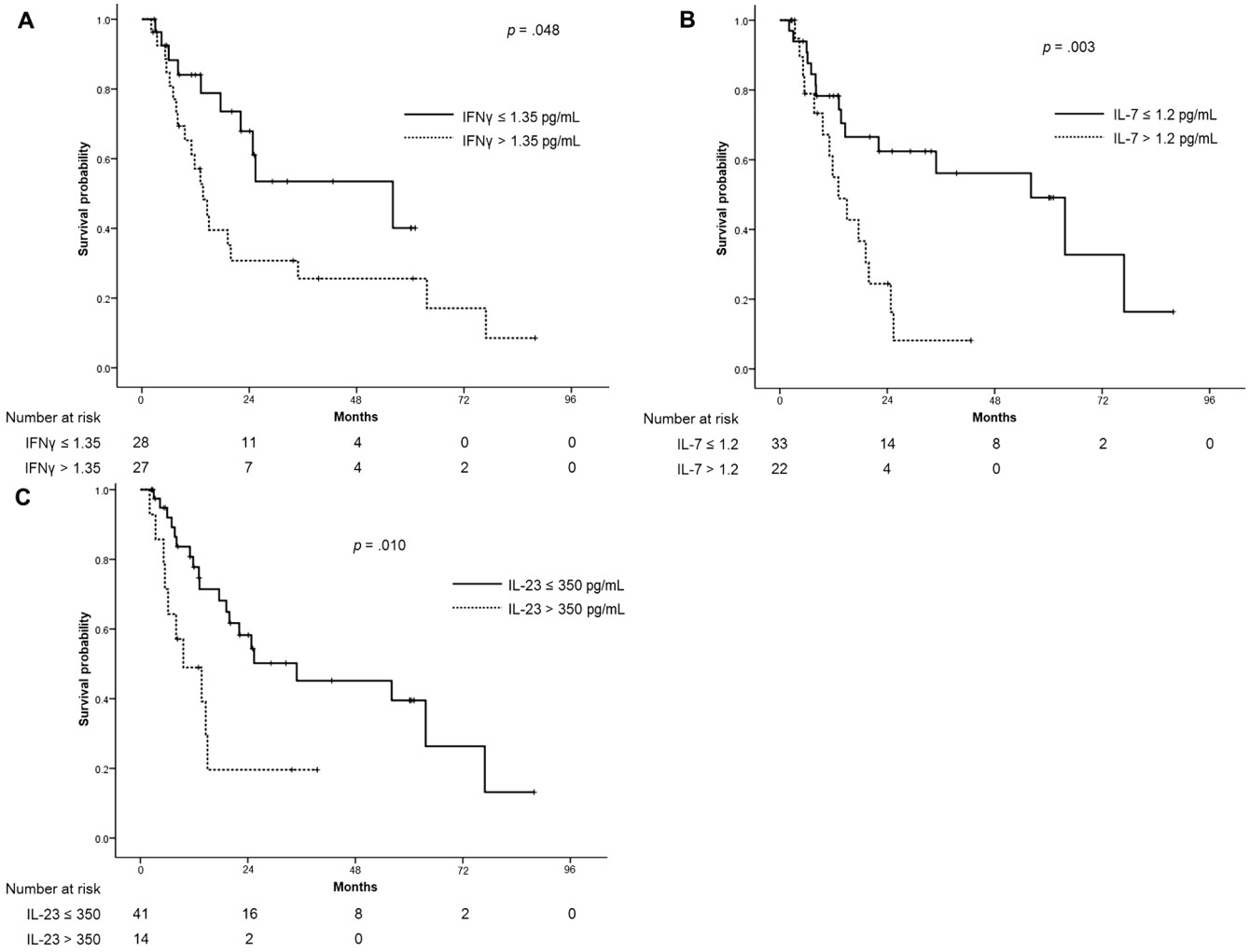

Fig. 3. Kaplan-Meier curves for overall survival of patients with POTCL according to the level of cytokines (N = 55). They were measured through multiplex chemokine assay. A, IFN-γ; B, IL-7; and C, IL-23. Log-rank test was used to compare the overall survival.

8 (any expression), IL-10 (> 0.5 pg/mL), IL-17 (any expression), IL-23 (> 250 pg/mL), IP-10 (> 20 pg/mL), MCP-1 (> 360 pg/mL), MIP-1β (> 230 pg/mL), and RANTES (> 100 pg/mL) were associated with shorter OS compared to their counterparts (Fig. 2). Among them, IFN-γ, IL-8, and RANTES were associated with a lower CR rate (Table 3). In terms of clinical parameters, ECOG performance scale and serum albumin showed significantly results. Multivariate analysis was not performed because the number of variables was large while the patient number was relatively small.

3.6. Serum cytokines and their associations with outcomes in PTCL-NOS

Three cytokines showed prognostic roles in this population. Twenty-seven patients (49.1%) expressed IFN-γ levels higher than 1.35 pg/mL, and their OS was significantly shorter (13.7, vs. 56.1 months, $P = 0.048$). These patients also showed a significantly lower CR rate (29.6% vs. 71.4%, $P = 0.002$). Higher IL-7 expression was associated with a lower OS. Twenty-two patients (40%) expressed IL-7 levels higher than 1.2 pg/mL and their OS was significantly shorter (13.1 vs. 56.1 months, $P = 0.003$). Those showing higher IL-23 levels (> 350 pg/mL, $N = 14$ (25.5%)) also showed shorter OS (9.6 vs. 34.9 months, $P = 0.01$) and a lower CR rate (14.3% vs. 63.4%, $P = 0.001$) (Fig. 3). For clinical parameters, increased serum LDH was associated with shorter OS. Multivariate analysis showed that only a high serum IL-7 concentration was associated with adverse OS (HR 3.861, 95% CI 1.701–8.772, $P = 0.001$) (Table 4).

4. Discussion

In this study, we analyzed 34 serum cytokines in 121 patients with AITL, ALK$^-$ ALCL, or PTCL-NOS. Compared to our previous study [12], a larger number of patients was analyzed over a longer period. Additionally, a larger number of cytokines was analyzed, as the previous study analyzed only 7 cytokines. We found that the profiles of each cytokine and their clinical implications differed between subgroups.

Compared to other subtypes, the AITL group had more cases with elevated serum levels of cytokines, as 55.4% of all available cases expressed any cytokine at significantly higher levels than in the ALK$^-$ ALCL (47.1%), and PTCL-NOS (50.2%) groups. Moreover, the mean levels of 7 cytokines (GROα, IFN-α, IL-7, MIP-1α, MIP-1β, RANTES, and SDF1α) were significantly higher than in the other subtypes. This is consistent with the observation that AITL patients generally have constitutional symptoms along with elevated inflammatory markers. However, most cytokines were not significantly associated with clinical outcomes; the only cytokine showing prognostic value was IL-10, as also demonstrated in our previous study. IL-10 has been suggested to promote lymphomagenesis through dysregulation of monocyte differentiation [5], aberrant activation of the JAK2 pathway [15], and down-regulation of antigen presentation inducing immune escape [16].

In ALK$^-$ ALCL, 9 cytokines showed clinical significance and were categorized into 2 groups. IL-8, IP-10, MCP-1, MIP-1β, and RANTES are chemokines that induce chemotaxis of inflammatory cells. IL-8 is a CXC-chemokine produced by macrophages and induces chemotaxis of

Table 4
Clinical outcomes of patients with PTCL-NOS.

	N (%)	Overall survival (median, 95% CI)	*P*	CR (*N*, rate%)	*P*
IFN-γ			0.048		0.002
≤1.35 pg/mL	28 (50.9)	56.1 (13.0–99.2)		20 (71.4)	
> 1.35 pg/mL	27 (49.1)	13.7 (9.5–17.9)		8 (29.6)	
IL-7			0.003		0.912
≤1.2 pg/mL	33 (60.0)	56.1 (29.4–82.8)		17 (51.5)	
> 1.2 pg/mL	22 (40.0)	13.1 (8.1–18.1)		11 (50.0)	
IL-23			0.010		0.001
≤350 pg/mL	41(74.5)	34.9 (1.0–68.8)		26 (63.4)	
> 350 pg/mL	14 (25.5)	9.6 (1.1–18.1)		2 (14.3)	
Age			0.415		0.228
≤60 years	31 (56.4)	34.9 (0.0–72.8)		18 (58.1)	
> 60 years	24 (43.6)	19.9 (9.5–30.3)		10 (41.7)	
ECOG PS			0.590		0.015
0–1	44 (80.0)	22.1 (14.8–29.4)		26 (59.1)	
2–3	11 (20.0)	11.1 (0.0–36.9)		2 (18.2)	
Ann Arbor stage			0.905		0.016
1–2	14 (25.5)	22.1 (12.4–31.8)		11 (78.6)	
3–4	41 (74.5)	24.8 (11.5–38.1)		17 (41.5)	
Extranodal site(s)			0.897		0.002
0–1	32 (58.2)	22.1 (13.7–30.5)		22 (68.8)	
More than 2	23 (41.8)	56.1 (0.0–116.4)		6 (26.1)	
Serum LDH			0.041		0.009
Within normal limit	24 (43.6)	56.1 (1.3–111.0)		17 (70.8)	
Increased	31 (56.4)	13.7 (10.8–16.6)		11 (35.5)	
ALC			0.729		0.362
≤600/μL	6 (10.9)	22.1 (0.0–47.9)		2 (33.3)	
> 600/μL	49 (89.1)	19.9 (6.9–32.9)		26 (53.1)	
Serum albumin			0.076		0.031
≤3.3 g/dL	14 (25.5)	8.0 (5.1–10.9)		2 (20.0)	
> 3.3 g/dL	41 (74.5)	24.8 (17.2–32.4)		26 (57.8)	

Multivariate analysis for overall survival

	Hazard ratio	95% CI	*P*
Increased LDH	1.416	0.612–3.279	0.416
IL-23 > 350 pg/mL	2.545	0.964–6.711	0.059
IL-7 > 1.2 pg/mL	3.289	1.453–7.444	0.004
IFN-γ > 1.35 pg/mL	1.350	0.512–3.559	0.545

neutrophils and angiogenesis. Neutrophils are involved in lymphomagenesis by producing proliferative cytokines such as APRIL [17] or by dysregulating the tumor microenvironment [18]. MCP-1 is a C-chemokine that is a potent chemoattractant for monocytes and T-cells. Several studies have reported the presence of this molecule in lymphoma patients [19], and its potential roles in lymphomagenesis may involve recruitment of tumor-associated macrophages. Other cytokines including IFNγ, IL-10, IL-17, and IL-23 are involved in the JAK/STAT pathway [20–22]. Our findings suggest a role for the tumor microenvironment and JAK/STAT pathway in ALK$^-$ ALCL.

Serum cytokine profiles of PTCL-NOS differ from those of AITL and ALK-negative ALCL. Thus, IFN-γ, IL-7, and IL-23 have prognostic impact. In contrast to the conventional perception that IFN-γ induces antitumor immunity, recent studies showed that it is involved in tumor progression by several means such as PD-L1 induction [23]. Additionally, increased serum levels of IFN-γ were associated with poor prognosis in patients with lymphoproliferative disorder [24]. IL-7 is well-known for its role in malignant T-cell neoplasms [25,26], and IL-7 depletion led to regression of malignant T-cells in a mouse xenograft model [27]. IL-23, as described above, is involved in the JAK/STAT pathway. Several roles for IL-23 have been suggested in the lymphomagenesis such as the stimulation of IFN-γ production [28] and suppression of natural killer cells [29].

5. Conclusions

Given that expression pattern and concentration of cytokines as well as their clinical implications differed according to the histologic subtype, again, it is emphasized that PTCL is a heterogeneous disease in biologic perspectives. In this regards, the current study provides preliminary evidence of precise approach of PTCL patients. Additionally, given that immunosuppressive features dominate in the tumor microenvironment of PTCL [30] and tumor progression is significantly contributed by non-tumor cells surrounding the tumor and secreted non-cellular components, disclosing the role of cytokines is essential to improve disease outcomes. In conclusion, the current study demonstrated that several cytokines related to the JAK pathway or tumor microenvironment have prognostic relevance, which is important for understanding the pathogenesis of PTCL and suggesting future treatment directions.

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