Original Article

Increased serum level of interleukin-6 correlates with negative prognostic factors in extranodal NK/T-cell lymphoma

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Background: Extranodal natural killer/T-cell lymphoma (ENKTL) is a rare subtype of non-Hodgkin lymphoma (NHL), characterized as mature T- and natural killer (NK)-cell lymphoma, which is more common in East Asia and Latin America than in other parts of the world. The overproduction of proinflammatory cytokines such as interleukin-6 (IL-6) plays an essential role in the development of lymphoma.

Methods: We measured serum IL-6 and IL-6 related cytokines of 65 newly diagnosed ENKTL patients to assess biomarkers for prognosis of ENKTL.

Results: Patients with high IL-6 (>15.920 mg/L) at diagnosis had more adverse clinical features. Patients with low IL-6 (≤15.920 mg/L) at diagnosis had better progression-free survival (PFS; P=0.002), overall survival (OS; P<0.001), and higher complete remission rates (P=0.001). IL-6 correlated with lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α). Multivariate analysis revealed Ann Arbor stage [P=0.001, risk ratio (RR) =6.011 (2.102–17.191)] and IL-6 [P=0.012, RR =2.367 (1.206–4.643)] to be independent prognostic factors for PFS. Multifactor analysis of OS revealed Ann Arbor stage [P=0.015, RR =3.600 (1.278–10.141)], IL-6 [(P=0.001), RR =3.565 (1.720–7.390)], and chemotherapy that not containing L-asparaginase [(P=0.009, RR =2.717 (1.252–5.780)] to be independent prognostic factors for shorter OS.

Conclusions: These results suggest serum IL-6 at diagnosis is predictive of prognosis for ENKTL, and IL-6 increase is activity during the pathogenesis of ENKTL and offers new insight into potential therapeutic strategies.

Keywords: Extranodal NK/T-cell lymphoma; increased serum IL-6; negative prognosis

Submitted Oct 17, 2019. Accepted for publication Feb 14, 2020.
doi: 10.21037/tcr.2020.03.49
View this article at: http://dx.doi.org/10.21037/tcr.2020.03.49

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTL) is a highly aggressive malignant tumor with a poor prognosis (1). It is more common in Asia and Latin America than in Europe and North America (2), and accounts for 5% to 10% of malignant lymphomas in China (3). ENKTLs are histologically characterized by localized invasion, necrosis, and Epstein-Barr virus (EBV) infection of neoplastic cells. These tumors are confined to the nose and upper respiratory tract in 60% to 90% of patients (4), but may also occur outside the nasal cavity (e.g., in skin, testis, small intestine, and muscle) (2) or as a disseminated disease

without any noticeable nasal involvement (5). Patients with extra-nasal ENKTL have a worse prognosis than those with nasal ENKTL (6).

Serum markers are related to tumor behavior. Some biomarkers - such as the plasma EBV DNA level at diagnosis (6), soluble interleukin 2 receptor (sIL2R) level (2,7), Chemokine (C-X-C motif) ligand 9 (CXCL9), CXCL10 (8), interleukin-15 (IL-15) (9), interleukin-2 (IL-2) (10), and interleukin 9 (IL-9) are associated with prognosis of ENKTL (11,12). In some hematologic malignancies, the presence of ferritin in the serum is the direct result of tumor activity (2). In addition, Ki67 index of greater than 50%, transformed tumor cells greater than 40%, an increased level of C-reactive protein (CRP) (13), anemia, and thrombocytopenia are used to predict the prognosis of ENKTL (6). However, serum level of IL-6 has been seldom interpreted in prognosis of ENKTL. IL-6 is a proinflammatory cytokine that promotes proliferation, survival, and activation of multiple lymphocyte lineages, the relation between IL-6 and ENKTL prognosis has not yet been clarified.

Methods

Patients

A retrospective cohort study was designed and patients with nasal ENKTL were systematically reviewed at the Department of Hematology of the First Affiliated Hospital of Zhejiang University between January 2010 and January 2018. A total of 236 newly diagnosed patients with ENKTL were enrolled in this study and 65 patients were selected. Inclusion criteria were (I) diagnosis of the World Health Organization classification of ENKTL; (II) CD3, CD56, and cytotoxic molecules were positive and CD20 was negative in situ hybridization; (III) no previous antitumor therapy; (IV) before treatment, serum samples were stored at the experimental center of the First Affiliated Hospital of Zhejiang University; and (V) complete follow-up results were available. Exclusion criteria were (I) diagnosis of other malignant tumors; (II) any medical coexisting problems that hindered the standard anti-tumor treatment; and (III) other subtypes of non-Hodgkin lymphoma (NHL), including acute myeloid/NK cell precursors of leukemia, naive NK cell lymphoma/precursor NK lymphocytic cell leukemia, aggressive NK cell leukemia, and peripheral T-cell lymphoma.

All the patients underwent physical examination, whole-body positron emission tomography/computed tomography CT (PET/CT) scan or magnetic resonance imaging (MRI) scan of head, neck, chest, abdomen and pelvis; routine blood examination; and blood biochemical examination. The study was approved by the Committee of the First Affiliated Hospital of Zhejiang University Medical School. All patients signed letters of informed consent before treatment. Clinical and laboratory characteristics were recorded including age, performance status, Ann Arbor stage, B symptoms, primary sites, sites of extranodal invasion, etc.

Treatment

Initial treatment of patients

The following treatment strategies were used: (I) early stage ENKTL patients received chemotherapy, followed by involved-field radiation therapy (IFRT). (II) Patients with advanced ENKTL received only chemotherapy. The non-L-asparaginase chemotherapy regimen consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and EPOCH (etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisone). Chemotherapy with L-asparaginase consisted of GELOX (gemcitabine, oxaliplatin L-asparaginase) or adjusted GELOX (14), SMILE (ifosfamide, methotrexate, L-asparaginase, and etoposide), CHOP-L (CHOP plus L-asparaginase) and DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin). Patients received at least two cycles of initial chemotherapy and at most to eight cycles. The total dose of radiation therapy was 50–60 Gy in five fractions (1.8–2.0 Gy each) per week.

Cytokine detection

Serum levels of IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α, and interferon-γ (IFN-γ) were measured by enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems). All venous blood samples were obtained from 65 patients with ENKTL. Samples were collected, centrifuged at 4 ℃, and frozen rapidly at –80 ℃ for further detection. The ELISA inspection was carried out according to instructions.

Evaluation of therapeutic efficiency

The treatment response was evaluated according to standardized criteria for NHL response (15). Patients were evaluated after two courses of chemotherapy.

Follow-up

After completion of treatment, the patients were evaluated

by hematologists. Follow-up intervals were established according to routine criteria. The OS is from the time of the initial diagnosis until the time of death or until the last follow-up. progression-free survival (PFS) is the time of diagnosis until disease progression, recurrence, death from any cause, or until the last follow-up.

Statistics

Data statistics included nonparametric mean difference tests for the Mann-Whitney U-test. The concentration of cutoff was determined by the receiver operating characteristic (ROC) curve analysis. The correlation among LDH, IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α, IFN-γ, and complete remission was analyzed by Chi-square test. The effects of various factors on OS and PFS were calculated by using the Kaplan-Meier and log-rank test methods. The correlation between the factors was examined by using of the Spearman test. COX regression was utilized to analyze the prognostic significance of multivariate variables.

Results

Patient characteristics

The clinical features of 65 patients (48 males and 17 females, with a median age of 47 years old) were presented in *Table 1*. Among these patients, 46 (70.8%) had good Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0–1), 44 (67.6%) had B symptoms (fever, unexplained temperature higher than 38 ℃, night sweats, or weight loss within 6 months more than 10%), and 42 (64.6%) were Ann Arbor stage III/IV. The primary site was nasal cavity in 32 patients (49.2%) and the other 33 patients (50.8%) had extranasal sites. Ki67 index in 17 patients (26.2%) was more than 50%. Hemophagocytic syndrome was found in 12 patients (18.5%). At diagnosis, the median serum ferritin level was 422 μg/L (range, 65.5–1,829.00 μg/mL), the median CRP level was 10.3 mg/L (range, 0.5–154 mg/L), the median IL-2 level was 0.40 pg/mL (range, 0.01–27.74 pg/mL), the median IL-6 level was 10.06 pg/mL (range, 0.10–1,176.97 pg/mL), the median interleukin 10 (IL-10) level was 6.13 pg/mL (range, 0.1–5,447.32 pg/mL), and the median tumor necrosis factor-α (TNF-α) level was 0.95 pg/mL (range, 0.01–1,233.04 pg/mL).

Table 1 General clinical characteristics of ENTKL patients

Clinical features	Median [range]	Number (N=65)	Percentage (%)
Age	47 [17–77]		
≤60		47	72.3
>60		18	27.7
Gender			
Male		48	73.8
Female		17	26.2
Ann Arbor stage			
I-II		23	35.4
III-IV		42	64.6
Primary site			
Nasal		32	49.2
Extranasal		33	50.8
B symptom			
No		21	32.3
Yes		44	67.6
ECOG PS			
0–1		46	70.8
≥2		19	29.2
IPI score			
0–1		19	29.2
≥2		46	70.8
Bone marrow involvement			
No		35	53.8
Yes		30	46.2
Lymph node involvement			
No		30	46.2
Yes		35	53.8
Ki67	0.7 [0.1–0.95]		
>0.5		17	26.2
≤0.5		48	73.8
EBV DNA (/L)	5×10E3 [0–7.61×10E6]		
Positive		36	55.4
Negative		15	29.4
Not detected		14	21.5

Table 1 (*continued*)

Table 1 (*continued*)

Clinical features	Median [range]	Number (N=65)	Percentage (%)
WBC (10E9/L)	3.8 [0.5–108.2]		
<4		34	52.3
≥4		31	447.7
HB (g/L)	113 [55–161]		
<110		31	47.7
≥110		34	52.3
PLT (10E9/L)	157 [5–519]		
<100		19	29.2
≥100		46	70.8
ALB (g/L)	37 [10.3–53.1]		
<35		25	38.5
≥35		40	61.5
Cr (μmol/L)	60 [4.7–179]		
≤85		61	93.8
>85		4	62
Hemophagocytosis			
No		53	81.5
Yes		12	18.5
Ferritin (μg/L)	422 [65.5–1,829.00]		
CRP (mg/L)	10.3 [0.5–154]		
IL-2 (pg/mL)	0.40 [0.01–27.74]		
IL-4 (pg/mL)	0.89 [0.01–20.48]		
IL-6 (pg/mL)	10.06 [0.10–1,176.97]		
IL-10 (pg/mL)	6.13 [0.1–5,447.32]		
IL-17A (pg/mL)	0.47 [0.01–63.27]		
TNF-α (pg/mL)	0.95 [0.01–1,233.04]		
IFN-γ (pg/mL)	2.09 [0.01–771.24]		

ENTKL, extranodal natural killer/T-cell lymphoma; CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ.

Receiver operating characteristic curve analysis for the optimal cutoff point of lactate dehydrogenase, CRP, ferritin, and cytokines

To determine the best cutoff value, CRP, ferritin, LDH, and cytokines were analyzed by the ROC curve (*Figure 1*).

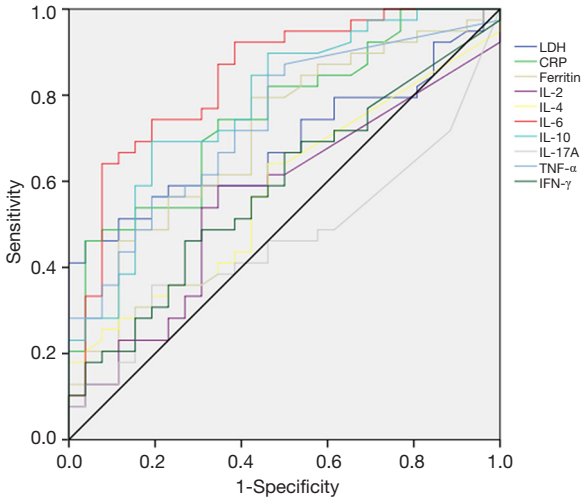

Figure 1 ROC curve analysis for the optimal cutoff point of serum LDH, CRP, ferritin, and cytokines. ROC, receiver operating characteristic; LDH, lactate dehydrogenase; CRP, C-reactive protein.

For the LDH curve, the area under the curve (AUC) was 0.688 (0.561–0.816), the most differentiated cutoff value was 548 U/L, and sensitivity and specificity were 0.462 and 0.968, respectively. For the CRP curve, the AUC was 0.754 (0.637–0.871), the most differentiated cutoff value was 25.35 μg/L, and the sensitivity and specificity were 0.462 and 0.962, respectively. For the ferritin curve, the AUC was 0.707 (0.578–0.835), the most differentiated cutoff value was 323.25 mg/L, and the sensitivity and specificity were 0.795 and 0.577, respectively. For the IL-6 curve, the AUC was 0.833 (0.728–0.937), the most differentiated cutoff value was 15.92 pg/mL, and the sensitivity and specificity were 0.641 and 0.920, respectively. For the IL-10 curve, the AUC was 0.769 (0.651–0.888), the most differentiated cutoff value was 6.145 pg/mL, and the sensitivity and specificity were 0.692 and 0.800, respectively. For the TNF-α curve, the AUC was 0.728 (0.604–0.852), the most differentiated cutoff value was 0.275 mg/L, and the sensitivity and specificity were 0.846 and 0.520, respectively (*Table 2*).

Efficacy and survival analysis

Chemotherapy was performed in 54 patients (83.1%), and the other 11 patients were treated with chemoradiotherapy. Among these patients, 45 (69.2%) received chemotherapy regimens containing L-asparaginase, and the remaining 20 (30.8%) received chemotherapy without L-asparaginase.

Table 2 Analysis for the optimal cutoff point of CRP, ferritin, LDH, and cytokines in serum

Variable	AUC	95% CI	P value	Cutoff value	Sensibility	Specificity
LDH	0.688	0.561–0.816	0.001	548 U/L	0.462	0.968
CRP	0.754	0.637–0.871	0.001	25.35 μg/L	0.462	0.962
Ferritin	0.707	0.578–0.835	0.005	323.25 mg/L	0.795	0.577
IL-2	0.552	0.408–0.696	0.487			
IL-4	0.570	0.429–0.711	0.346			
IL-6	0.833	0.728–0.937	<0.001	15.920 pg/mL	0.641	0.920
IL-10	0.769	0.651–0.888	<0.001	6.145 pg/mL	0.692	0.800
IL-17A	0.481	0.339–0.622	0.794			
TNF-α	0.728	0.604–0.852	0.002	0.275 pg/mL	0.846	0.520
IFN-γ	0.588	0.446–0.729	0.239			

LDH, lactate dehydrogenase; CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ.

Table 3 Efficacy analysis of factors on CR rates

Factor	Group	Number	CR rate (%)	P value
Gender	Female	17	76	0.030
	Male	48	46	
Age	≤60 years	47	60	0.139
	>60 years	18	39	
Ki67	≤0.5	17	76	0.030
	>0.5	48	46	
LDH	≤548 U/L	46	65	0.004
	>548 U/L	19	26	
ENV-DNA titer	≤3.525×10E4/L	32	66	0.006
	>3.525×10E4/L	19	26	
CRP	≤25.35 mg/L	46	63	0.020
	>25.35 mg/L	19	32	
Ferritin	≤323.25 μg/L	23	78	0.003
	>323.25 μg/L	42	40	
IL-6	≤15.92 pg/mL	38	71	0.001
	>15.92 pg/mL	27	30	
IL-10	≤6.145 pg/mL	33	73	0.002
	>6.145 pg/mL	32	34	
TNF-α	≤0.275 pg/mL	19	53	0.901
	>0.275 pg/mL	46	54	

LDH, lactate dehydrogenase; CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α; CR, complete remission.

Bone marrow transplantation was performed in 4 patients (6.2%), 35 patients (53.8%) achieved complete remission (CR), 6 patients (9.2%) achieved partial remission (PR), 6 patients (9.2%) were evaluated as having stable disease (SD), and 18 patients had progressive disease (PD).

CR rates for females and males were 76% and 46%, respectively (P=0.030). Patients with Ki-67 index more than 0.5 achieved a CR rate of 46%; Otherwise, CR rate was 76% (P=0.030). CR rate of patients with nasal primary sites was 78% and patients with extranasal sites was 30% (P<0.001). For LDH ≤548 U/L, the CR rate was 65%, and for LDH >548 U/L, CR rate was 26%, with significant difference (P=0.004). For Ferritin ≤323.25 and >325.25 μg/L, CR rates were 78% and 40%, respectively, with significant difference (P=0.003). For IL-6 ≤15.920 pg/mL and IL-6 >15.920 pg/mL, CR rates were 71% and 30%, respectively (P=0.001). For IL-10 ≤6.145 pg/mL and >6.145 pg/mL, CR rates were 73% and 34% (P=0.002) (*Table 3*).

Survival analysis

The median PFS was 282.23 days (9.41 months), and the median OS was 379.28 days (12.64 months) (*Figures 2* and *3*). Patients with Ann Arbor stage I-II and III-IV had significant differences in PFS and OS (P<0.001 and P=0.001, respectively). There were significant differences in PFS and OS in patients with nasal cavity ENKTL and extranasal ENKTL (P=0.001 and P=0.002, respectively). Patients with ECOG Performance Status (ECOG PS) score 0–1 and higher than 2 had significant differences in

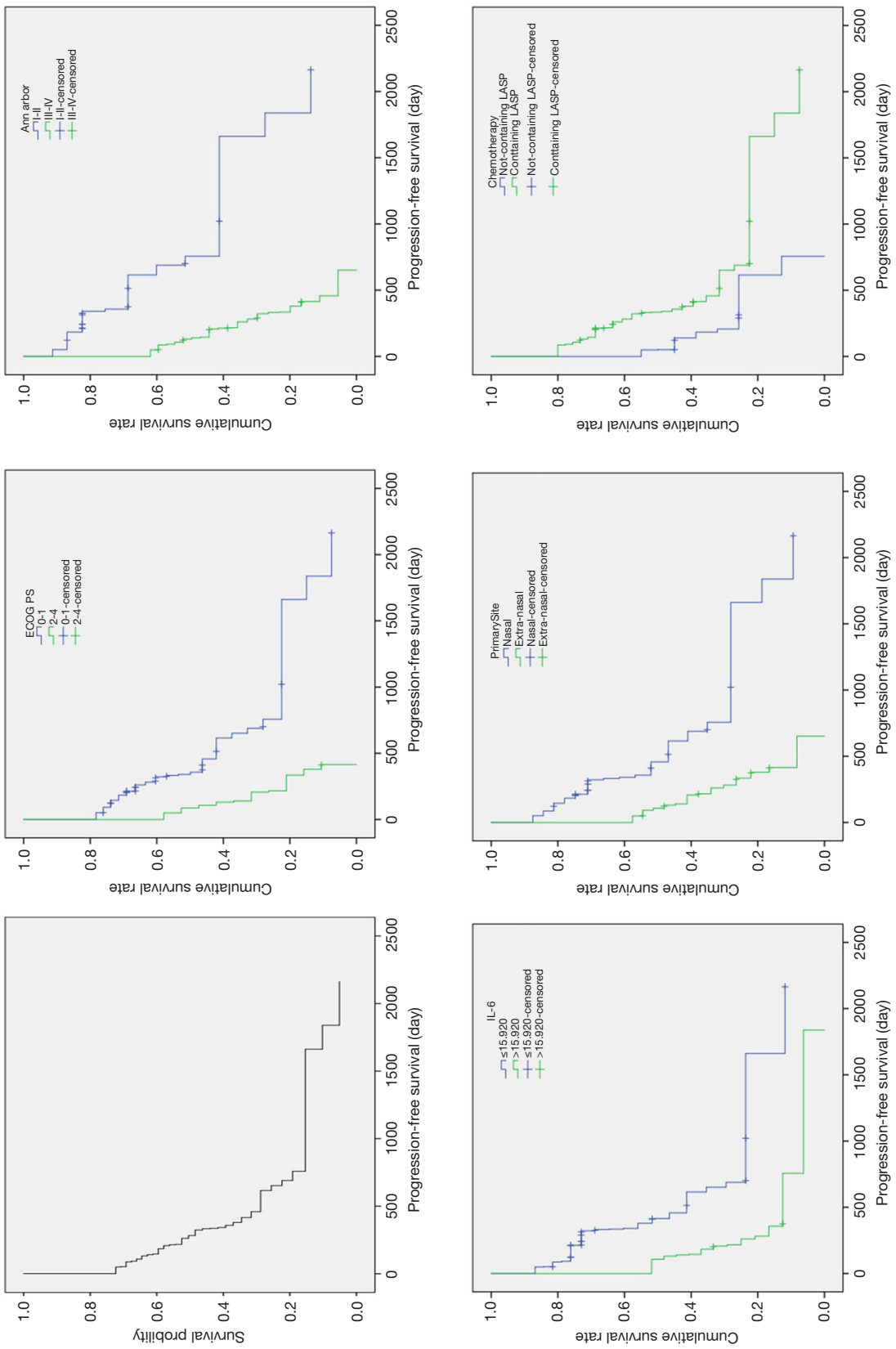

Figure 2 Progression-free survival analysis of factors on ENTKL patients. ENTKL, extranodal natural killer/T-cell lymphoma.

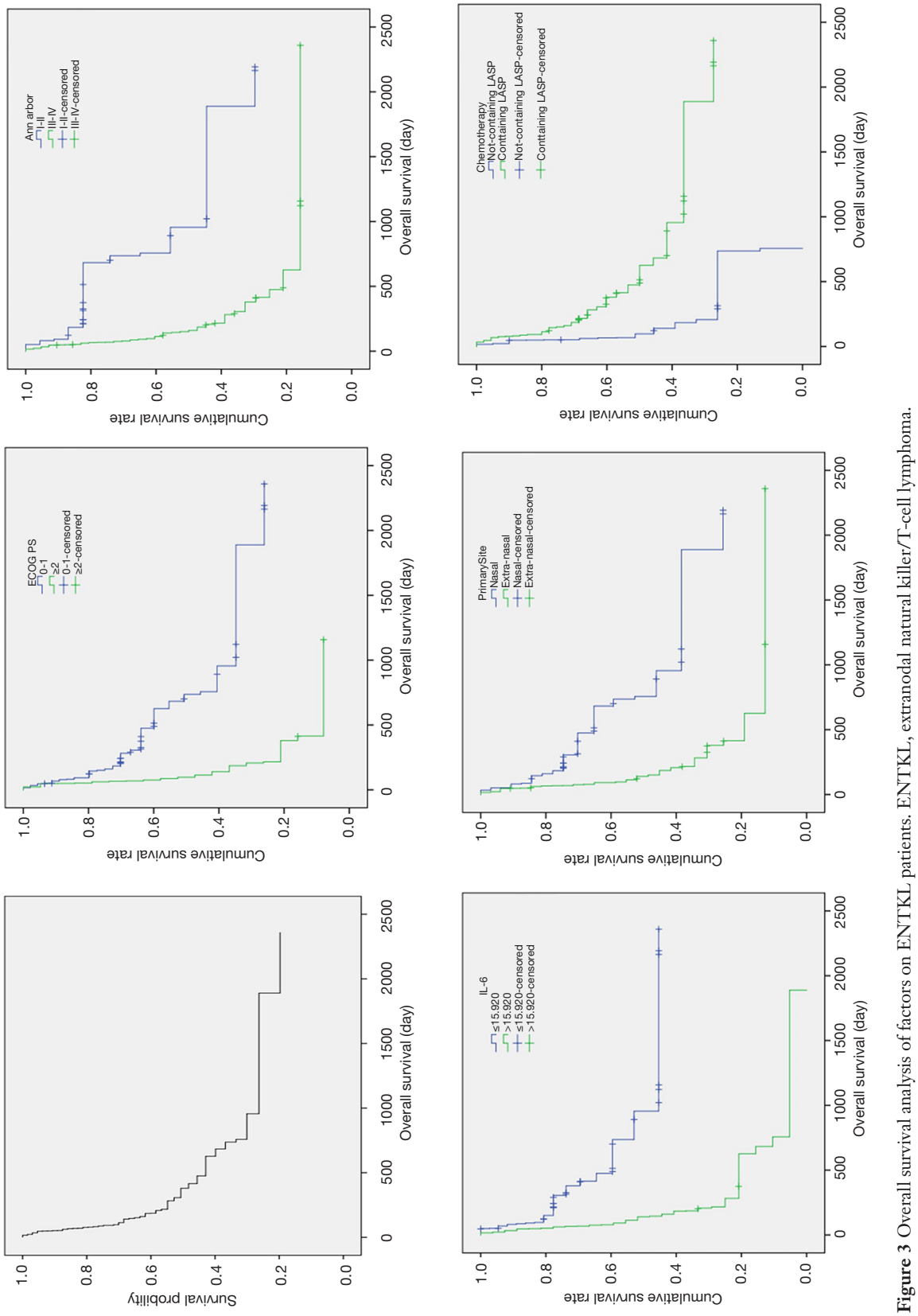

Figure 3 Overall survival analysis of factors on ENTKL patients. ENTKL, extranodal natural killer/T-cell lymphoma.

PFS and OS (P=0.001 and P<0.001, respectively). Patients treated with a chemotherapy regimen, with or without L-asparaginase, had significant differences in PFS and OS (P=0.021 and P=0.001, respectively). Patients with ferritin >323.25 μg/L and ferritin ≤323.25 μg/L, had significant differences in PFS and OS (P=0.001 and P<0.001, respectively). Patients with CRP ≤25.35 mg/L and CRP >25.35 mg/L had significant differences in PFS and OS (P=0.005 and P<0.001, respectively). Patients with IL-6 ≤15.920 pg/mL and IL-6 >15.920 pg/mL had significant differences in PFS and OS (P=0.002 and P<0.001, respectively). Patients with IL-10 ≤6.145 pg/mL and IL-10 >6.145 pg/mL had significant differences in PFS and OS (P=0.003 and P=0.001, respectively). There were no significant differences in PFS (P=0.086) and OS (P=0.806) in patients with TNF-α ≤0.275 pg/mL and TNF-α >0.275 pg/mL (*Table 4* and *Figures 2* and *3*).

Correlation analysis

A correlation analysis of LDH, ferritin, CRP, IL-6, and IL-10 was performed. Because the data are not a normal distribution, a Spearman correlation was carried out. There was a significant correlation between IL-6 and LDH, IL-6 and ferritin, IL-6 and CRP, IL-6 and IL-10. The correlation coefficient between IL-6 and LDH was 0.282, which was significant (P=0.023). The correlation coefficient between IL-6 and IL-10 was 0.544 (P<0.001). The correlation coefficient between IL-6 and ferritin was 0.363 (P=0.003). The correlation coefficient between IL-6 and CRP was 0.282, which was significant (P=0.023). Therefore, IL-6, Ann Arbor stage, primary sites, ECOG PS scores, and chemotherapy were included in the multivariate analysis.

Multivariate analysis

In the multivariate analysis of PFS, Ann Arbor stage [P=0.001, RR =6.011 (2.102–17.191)] and IL-6 [P=0.012, RR =2.367 (1.206–4.643)] were independent prognostic factors. In multifactor analysis of OS, Ann Arbor stage [P=0.015, RR =3.600 (1.278–10.141)], IL-6 [P=0.001, RR =3.565 (1.720–7.390)], and non-L-asparaginase chemotherapy [P=0.009, RR =2.717 (1.252–5.780)] were independent prognostic factors.

Discussion

This study demonstrated that an increased IL-6 level was significantly associated with poor survival outcomes with ENKTL patients. Our findings illustrated serum levels of cytokines IL-6 and IL-10, CRP, ferritin, LDH were related with prognosis of ENKTL, and IL-6 was correlated with the other factors. Ann Arbor stage I-II and III-IV, nasal cavity ENKTL and extra nasal ENKTL, ECOG Performance Status (ECOG PS) score 0–1 and higher than 2, chemotherapy with or without L-asparaginase had significant differences in PFS and OS of ENTKL patients. Therefore, we built a model with IL-6 level, Ann Arbor stage, primary site, ECOG PS and chemotherapy to predict prognosis for ENKTL.

Vose *et al*. reported an association among serum ferritin level, albumin, and CRP level. However, a multivariate model that used ferritin, albumin, and CRP levels did not predict patient outcome (16). Thus, the combination of inflammation factors could not predict prognosis. For this reason, we performed a correlation analysis of LDH, ferritin, CRP, IL-6, and IL-10, and found a significant correlation among IL-6 and the other serum markers.

Gene expression profiles of ENKTL tumor cells showed overexpression of chemokines and cytokines compared to normal NK cells (17). In patients with ENKTL, elevated serum levels of VEGF and IL-6 may be related to activation of the PI3K/Akt and JAK/STAT3 pathways in lymphoma cells, which in turn results in increased transcription of VEGF and IL-6 by phosphorylation of Akt and STAT3 (18). Whereas ENKTL is frequently associated with inflammation at diagnosis, the paracrine effect of tumor microenvironment can also be caused by the secretion of VEGF and IL-6 from inflammatory bone marrow cells and lymphocytes (19). Kim *et al*. reported that IL-6 correlated with OS in patients with ENKTL (20). Our study determined that IL-6 was an independent factor of PFS and OS in ENKTL patients.

In some hematologic malignancies, serum ferritin is directly related to tumor activity. Tisi *et al*. (21) reported that elevated level of ferritin was associated with increased hepcidin levels, which in turn indicated disease activity in patients with lymphoma. Patients with high ferritin level had a low CR rate and shorter PFS and OS (16), which was consistent with our findings (22).

Pretreatment serum IL-10 levels were believed to be associated with progression and prognosis of ENKTL. Moreover, IL-10 is an important immune-related cytokine that limits antitumor immunity, proliferation, and anti-apoptosis (14). Gravisaco *et al*. suggested that IL-10 was a key factor in the growth of mouse T-cell lymphoma cells (23). IL-10 also supports and enhances tumorigenicity (24) of

Table 4 Univariate and multivariate analysis of factors associated with progression-free survival and overall survival of ENTKL patients

Factor	Progression-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	P	HR	95% CI	P	RR	95% CI	P	HR	95% CI	P	RR	95% CI
Age												
≤60												
>60	0.634	0.851	0.439–1.652				0.830	1.080	0.535–2.181			
Gender												
Female												
Male	0.924	1.032	0.546–1.947				0.728	1.129	0.569–2.241			
Ann Arbor stage												
I-II												
III-IV	<0.001	5.664	2.409–113.316	0.001	6.011	2.102–17.191	0.001	3.515	1.637–7.546	0.015	3.600	1.278–10.141
Primary site												
Nasal												
Extranasal	0.001	3.035	1.571–5.864	0.778	11.127	0.49–2.591	0.002	2.870	1.479–5.567	0.865	1.086	0.420–2.809
B symptom												
No												
Yes	0.180	1.551	0.817–2.945				0.075	1.934	0.936–3.995			
ECOG PS												
0–1												
≥2	0.001	2.882	1.521–5.460	0.772	1.121	0.518–2.425	<0.001	3.348	1.736–6.457	0.475	1.383	0.568–3.367
IPI score												
0–1												
≥2	0.025	2.262	1.107–4.625				0.125	1.795	0.850–3.791			
Chemotherapy regime												
No L-asparaginase	0.021	2.096	1.116–3.937	0.061	1.969	0.970–3.984	0.001	3.077	1.577–5.988	0.009	2.717	1.252–5.780
L-asparaginase												
WBC (10E9/L)												
<4												
≥4	0.108	0.609	0.332–1.114				0.078	0.554	0.287–1.069			

Table 4 (*continued*)

Table 4 (*continued*)

Factor	Progression-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	P	HR	95% CI	P	RR	95% CI	P	HR	95% CI	P	RR	95% CI
HB (g/L)												
<110												
≥110	0.869	0.952	0.533–1.703				0.629	0.856	0.457–1.606			
PLT (10E9/L)												
<100												
≥100	0.054	0.533	0.281–1.011				0.023	0.459	0.235–0.898			
LDH (U/L)												
≤548												
>548	<0.001	4.371	2.157–8.856				<0.001	4.669	2.292–9.510			
Hemophagocytosis												
No												
Yes	0.004	2.918	1.412–6.031				0.001	3.729	1.755–7.921			
CRP (mg/L)												
≤25.35												
>25.35	0.005	2.371	1.290–4.356				<0.001	3.564	1.883–6.748			
Ferritin (μg/L)												
≤323.25												
>323.25	0.001	3.258	1.695–6.612				<0.001	5.257	2.232–12.382			
IL-6 (pg/mL)												
≤15.92												
>15.92	0.002	2.587	1.427–4.690	0.012	2.367	1.206–4.643	<0.001	4.214	2.166–8.196	0.001	3.565	1.72–7.39
IL-10 (pg/mL)												
≤6.145												
>6.145	0.003	2.531	1.373–4.667				0.001	4.419	2.168–9.005			
TNF-α (pg/mL)												
≤0.275												
>0.275	0.086	2.035	0.903–4.586				0.806	2.155	0.896–5.181			

ENTKL, extranodal natural killer/T-cell lymphoma; CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α.

T-cell lymphoma in the autocrine mode (25).

Treatment options for ENKTL included: radiotherapy, chemotherapy, chemotherapy followed by involved-field radiotherapy (IFRT), and hematopoietic stem cell transplantation (HSCT). ENKTL is sensitive to radiation therapy, and radiotherapy is the main treatment for stage I/II nasal NK/T cell lymphoma. Although a high remission rate can be achieved by radiotherapy alone, patients nonetheless experience a high rate of recurrence. Chemotherapy followed by IFRT is the standard treatment for ENKTL. L-asparaginase is regarded as the most important drug in treatments for advanced ENKTL. A meta-analysis showed that the use of L-asparaginase was associated with better overall response rate (ORR) and CR rates in both localized and systemic ENKTL (26). Pokrovsky *et al*. (27) reported a meta-analysis of L-asparaginase in newly diagnosed ENKTL, revealing that L-asparaginase-containing regimens were beneficial for early and advanced ENKTL, which corresponded to our findings.

The international prognostic index (IPI) considers patient age, disease stage, serum LDH level, extranodal lesion site numbers, and ECOG PS. In ENKTL, nearly 60% of patients belong to the low-IPI-risk group (0–1 points), but nevertheless show significant heterogeneity. In our study, a large number of our patients had advanced Ann Arbor stage and a high IPI score. Kim *et al*. (28) identified four risk factors (age, stage, non-nasal type and distant lymph-node involvement) that were independently prognostic of OS and PFS (29). Also, our study showed that non-nasal type ENKTL was a negative prognosis factor for PFS and OS.

In sum, our findings confirmed the relation between IL-6 and several clinical features of ENKTL. We concluded that serum IL-6, which can be easily measured in clinical practice, is an independent prognostic factor for this disease and offers a new insight into potential therapeutic strategies such as blockade of IL-6. Future prospective studies are warranted to confirm our findings.

Acknowledgments

The authors thank the patients and their families and all the investigators, including the physicians, nurses, and laboratory technicians in this study.
Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.03.49). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Committee of the First Affiliated Hospital of Zhejiang University Medical School (No. IIT20200115A). All patients signed letters of informed consent before treatment.

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Cite this article as: Bao C, Zhou D, Zhu L, Qian W, Ye X. Increased serum level of interleukin-6 correlates with negative prognostic factors in extranodal NK/T-cell lymphoma. Transl Cancer Res 2020;9(4):2378-2389. doi: 10.21037/tcr.2020.03.49

