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Ifosfamide, methotrexate, etoposide, and prednisolone plus L-asparaginase as a first-line therapy in stage III/IV NK/T-cell lymphoma, nasal type

III/IV 기 NK/T 세포 림프종에서 ifosfamide, methotrexate, etoposide, prednisone 및 L-asparaginase 복합항암화학요법의 치료성적

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by

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ABSTRACT

Introduction: The prognosis of patients with stage III/IV NK/T-cell lymphoma (NTCL) is extremely poor. Although L-asparaginase (L-asp) is effective for NTCL, its significance has not been clearly demonstrated. In addition, there are few studies comparing treatment outcomes in stage III/IV NTCL. This study evaluated the efficacy of L-asp-based chemotherapy and prognostic factors in stage III/IV NTCL.

Patients and Methods: Seventy patients with newly diagnosed stage III/IV NTCL were enrolled between January 2000 and February 2013. Patients received ifosfamide, etoposide, methotrexate, and prednisolone (IMEP) plus L-asp (N=22) or combination chemotherapy without L-asp (N=48) as a first-line treatment. Clinical prognostic factors, treatment outcomes, and prognostic scores were compared between the groups.

Results: After a median follow-up period of 12.8 months (range, 1.1-186.6 months), median overall survival (OS) and progression-free survival (PFS) were 11.3 months and 5.6 months, respectively. Treatment outcomes were superior in patients treated with IMEP plus L-asp compared to those

treated with chemotherapy without L-asp (overall response rate 90.0% vs. 34.8%, P < 0.001; complete remission rate 65.0% vs. 21.7%, P = 0.001). The OS and PFS were significantly higher for the IMEP plus L-asp group compared with the chemotherapy without L-asp group. In a multivariate analysis, use of chemotherapy without L-asp was an independent predictor for reduced OS (hazards ratio (HR) = 2.18, 95% confidence interval (CI) 1.08-4.40; P = 0.030) and PFS (HR = 2.29, 95% CI 1.22-4.29; P = 0.010).

Conclusions: IMEP plus L-asp is active against stage III/IV NTCL, and it is an independent predictor for improved survival.

Keywords: ifosfamide, methotrexate, etoposide, prednisolone, L-asparaginase, and extranodal NK/T-cell lymphoma, nasal type.

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LIST OF ABBREVIATIONS

CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisolone

CI: Confidence interval

COPBLAM-V: Cyclophosphamide, vincristine, doxorubicin, bleomycin, procarbazine, and prednisolone

CR: Complete remission

Dex: Dexamethasone

DFS: Disease-free survival

ECOG PS: Eastern Cooperative Oncology Group performance status

HR: Hazard ratio

Hyper-CVAD: Cyclophosphamide, vincristine, doxorubicin, and dexamethasone

IMEP: Etoposide, ifosfamide, methotrexate, and prednisolone

IPI: International prognostic index

L-asp: L-asparaginase

LDH: Lactate dehydrogenase

Met: Methotrexate

NUAT: Non-upper aerodigestive tract

ORR: Overall response rate

OS: Overall survival

PFS: Progression-free survival

PR: Partial remission

SMILE: dexamethasone, methotrexate, ifosfamide, L-asp, and etoposide

UAT: Upper aerodigestive tract

INTRODUCTION

NK/T-cell lymphoma (NTCL) is defined as a distinct clinicopathologic disease in the World Health Organization (WHO) classification (1). It is most common in Asia and rare in Western populations. In Korea, it accounts for 6.3% of all non-Hodgkin's lymphoma with a male preponderance.

Patients with stage III/IV NTCL follow a very aggressive clinical course (2), and long-term outcomes with conventional combination chemotherapy are unsatisfactory. Because NTCL cells frequently express p-glycoprotein (3), which leads to multidrug resistance (MDR), anthracycline-based combination chemotherapy has limited activity in the treatment of NTCL. Therefore, non-anthracycline-based chemotherapy regimens including ifosfamide, etoposide, methotrexate, and prednisolone (IMEP) have been used in NTCL (4). In addition, L-asparaginase (L-asp), which is not affected by MDR, demonstrated anti-tumor activity against NK cell tumors in vitro (5). Recent phase II studies demonstrated the efficacy of L-asp-based combination chemotherapy in newly-diagnosed

stage IV or refractory NTCL (6-8). Nearly 80% of patients with stage IV or refractory/relapsed NTCL responded to a L-asp-based regimen with a complete response (CR) rate of 45-66%. Although combination chemotherapy is the standard treatment for advanced NTCL, there have been no studies to compare different chemotherapy regimens in stage III/IV NTCL. In addition, the prognostic significance of L-asp-based regimens has not been clearly elucidated in a relatively homogenous NTCL subset. Therefore, this study was conducted to evaluate the efficacy of L-asp-based combination chemotherapy and prognostic factors in advanced stage III/IV NTCL.

PATIENTS AND METHODS

Patients

A total of 70 patients who were newly diagnosed with NTCL between January 2000 and February 2013 were retrospectively identified from Seoul National University Hospital, Seoul National University Bundang Hospital, and Seoul National University Boramae Medical Center using the following inclusion criteria: 1) pathologically confirmed NTCL according to the WHO criteria (9, 10); 2) previously untreated, stage III/IV NTCL; and 3) received chemotherapy with curative intent. Patients who received radiotherapy or surgery alone (N=7) or a less intensive chemotherapy regimen (N=6) were excluded. The staging work-up included complete blood count, blood chemistry including lactate dehydrogenase (LDH), computed tomography (CT) of the neck, chest, and abdomen, bone marrow examination, and otolaryngologic examination of upper aerodigestive tract (UAT). UAT-NTCL was defined as a primary tumor involving the nasal cavity, nasopharynx, oral cavity, oropharynx, and hypopharynx whereas non-UAT

(NUAT)-NTCL referred to a primary tumor outside the UAT (11). Clinical demographics and prognostic factors were retrieved including age, sex, B symptoms, Eastern Cooperative Oncology Group performance status (ECOG PS), serum LDH level, Ann Arbor stage, number of extranodal sites, and International Prognostic Index (IPI) score (12). This study was reviewed and approved by the Institutional Review Board of each participant center and was conducted in accordance with the precepts established by the Declaration of Helsinki.

Treatment and response evaluation

All patients received first-line chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP, N=15); cyclophosphamide, vincristine, doxorubicin, bleomycin, procarbazine, and prednisolone (COPBLAM-V, N=4); cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD, N=1); IMEP (N=28); or IMEP plus L-asp (N=22). CHOP, COPBLAM-V, and Hyper-CVAD were anthracycline-based or CHOP-like regimens. Treatment was given until disease progression, unacceptable toxicities, or

patient's refusal. Four patients received stem cell transplantation at relapse.

The conventional IMEP regimen consists of ifosfamide at a dose of 1.5 g/m2 intravenously on days 1 to 3 with adequate hydration of 2 liters of half-saline per day and mesna to prevent hemorrhagic cystitis; methotrexate at a dose of 30 mg/m2 intravenously on days on 3 and 10; etoposide at a dose of 100 mg/m2 intravenously on days 1 to 3; and prednisolone at a dose of 60 mg/m2 orally on days 1 to 5, every 3 weeks. IMEP plus L-asp derived from Escherichia coli was administered as follows: IMEP plus L-asp at a dose of 6,000 IU/m2 on days 4, 6, 8, 11, 13, and 15 before Jan 2010 (N=7) and modified IMEP plus L-asp (methotrexate 30 mg/m2 on day 4 and L-asp 6,000 IU/m2 on days 1, 3, 5, 7, 9, and 11 after Jan 2010; N=15).

Clinical responses were assessed by physical and otolaryngologic examinations and CT scans using the response criteria for lymphoma (13). Adverse events were assessed according to the NCI-CTCAE version 3.0.

Statistical analysis

Clinicopathologic variables were compared between the groups by Pearson chi-square or Fisher exact tests, as appropriate. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the last follow-up visit. Progression-free survival (PFS) time was measured from the date of initial treatment to the date of disease progression, death, or the last follow-up visit. Disease-free survival (DFS) was calculated from the date of CR to the first evidence of relapse. Survival curves were derived by the Kaplan-Meier method (14). Comparison of survivals was performed using the log rank test. Univariate and multivariate analyses of independent factors for survival were performed using the Cox proportional hazard model (15). Variables with clinical significance and a significance level of < 0.05 were used for covariate entry. Variables with a P-value > 0.10 were removed during a backward stepwise analysis. All statistical tests were two-sided, with significance defined as $P < 0.05$. All analyses were performed using SPSS, version 21.0 (IBM Corporation, Armonk, New York).

RESULTS

Patients' characteristics

Patients' characteristics are summarized in Table I. The median age was 48.5 years (range, 18–73 years), and 48 patients (68.6%) were male. Half of the patients presented with UAT involvement with dissemination to lymph nodes (n=6), bone marrow (n=15), skin (n=5), gastrointestinal (GI) tract (n=3), soft tissues (n=5), central nervous system (n=4), lung (n=3), adrenal gland (n=1), bone (n=1), and orbit (n=1). NUAT-NTCL involved lymph nodes (n=9), bone marrow (n=10), skin (n=11), GI tract (n=4), soft tissues (n=4), central nervous system (n=1), lung (n=5), liver (n=1), and adrenal gland (n=1). Nearly two-thirds of the patients had systemic symptoms and three-fourths had high-intermediate and high IPI risk scores.

Table 1. Patients' characteristics

Characteristics	No. of patients (%)
Age	
≤ 60 years	55 (78.6)

> 60 years	15 (21.4)
Presentations	
UAT	35 (50.0)
NUAT	35 (50.0)
B symptoms	
No	22 (31.4)
Yes	48 (68.6)
Ann Arbor stage	
III	4 (5.7)
IV	66 (94.3)
LDH level	
Normal	12 (17.1)
Elevated	58 (82.9)
ECOG Performance status	
0-1	44 (62.9)
≥ 2	26 (37.1)
Number of extranodal sites	
0-1	16 (22.9)
≥ 2	54 (77.1)
IPI scores	
0-1	4 (5.7)
2	12 (17.1)
3	26 (34.1)
4-5	28 (40.0)

Treatment outcomes according to the first-line chemotherapy

Sixty-six patients were eligible for response evaluation. Among patients with chemotherapy without L-asp, there were no differences in ORR and CR rates between anthracycline-treated and IMEP-treated groups (ORR, 26.3% vs. 40.7%, P = 0.312; CR, 15.8% vs. 25.9%, P = 0.488). Similar treatment outcomes were observed in patients treated with anthracycline-based regimens, regardless of the regimen (data not shown). However, higher ORR and CR rates were observed in patients treated with IMEP plus L-asp compared with those treated with chemotherapy without L-asp (ORR 90.0% vs. 34.8%, P < 0.0001; CR 65.0% vs. 21.7% P = 0.001). Clinical factors and IPI risks were relatively well balanced between the treatment groups except for higher frequencies of UAT presentations and better ECOG PS in the IMEP plus L-asp group (Table II). Hematologic toxicities consisting of grade 3/4 leukopenia and neutropenia were the most frequent adverse events of the IMEP plus L-asp group. Nine patients (41%) experienced ≥ grade 3 febrile neutropenia without death events. Grade 3 or 4 allergic reactions due to L-asp were observed in four patients (18%).

Table 2. Clinical findings and treatment outcomes based on initial treatment modalities

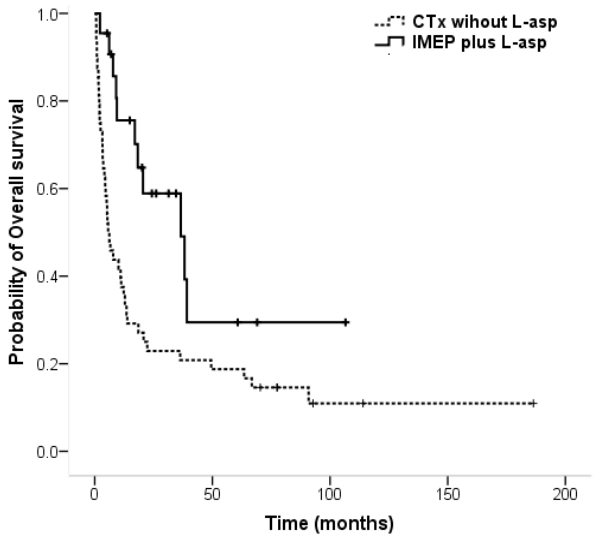
Clinical factors and outcomes		Chemotherapy without L-asp N = 48 (%)	IMEP plus L-asp N = 22 (%)	*P*-value
Cycles	Median (Range)	3 (1-6)	6 (1-8)	0.001
Age	≤ 60 years > 60 years	35 (72.9) 13 (27.1)	20 (90.9) 2 (9.1)	0.121
Presentations	UAT NUAT	18 (37.5) 30 (62.5)	17 (77.3) 5 (22.7)	0.004
B symptoms	No Yes	12 (25.0) 36 (75.0)	10 (45.5) 12 (54.5)	0.087
LDH level	Normal Elevated	6 (12.5) 42 (87.5)	6 (27.3) 16 (72.7)	0.128
ECOG PS	0-1 ≥ 2	26 (54.2) 22 (45.8)	18 (81.8) 4 (18.2)	0.034
Number of Extranodal sites	0-1 ≥ 2	12 (25.0) 36 (75.0)	4 (18.2) 18 (81.8)	0.760
IPI scores	0-2 3-4	8 (16.7) 40 (83.3)	8 (36.4) 14 (63.6)	0.068
Response rate		34.8% (16/46)	90.0% (18/20)	< 0.001
CR rate		21.7% (10/46)	65.0% (13/20)	0.001
OS	median (months) 1-year OS (%)	5.4 37.5%	36.6 75.6%	0.006
PFS	median (months) 1-year PFS (%)	3.2 16.7%	10.1 43.3%	0.002
DFS	median (months)	5.8	10.7	0.128

Survival analysis

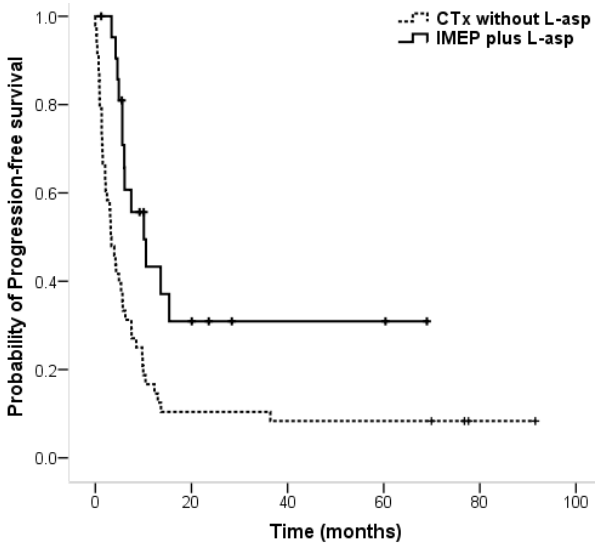
After a median follow-up of 12.8 months (range, 1.1-186.6 months), median OS, PFS, and DFS were 11.3 months, 5.6 months, and 8.0 months, respectively. The OS and PFS times were significantly higher for the IMEP plus L-asp group compared with the chemotherapy without L-asp group (Table II, Figure 1A-B). The IMEP plus L-asp group showed a tendency toward prolonged DFS (Figure 1C).

Figure 1. Kaplan-Meier plots of survivals of all NTCL patients according to the first-line chemotherapy

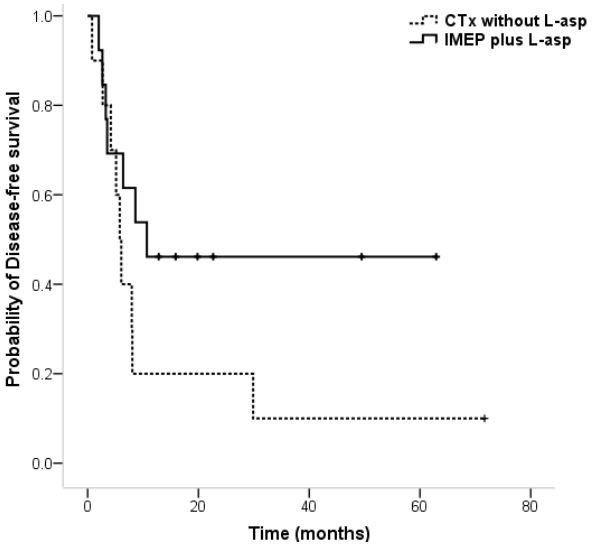
(A) **Kaplan-Meier plots of OS of all NTCL patients according to the first-line chemotherapy**



(B) Kaplan-Meier plots of PFS of all NTCL patients according to the first-line chemotherapy



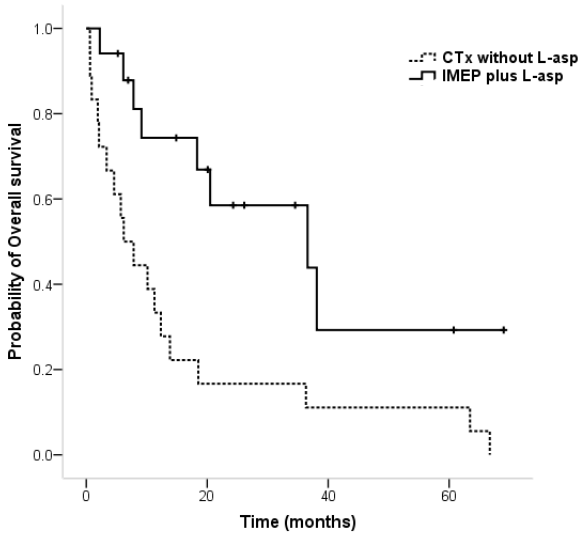
(C) Kaplan-Meier plots of DFS of all NTCL patients according to the first-line chemotherapy



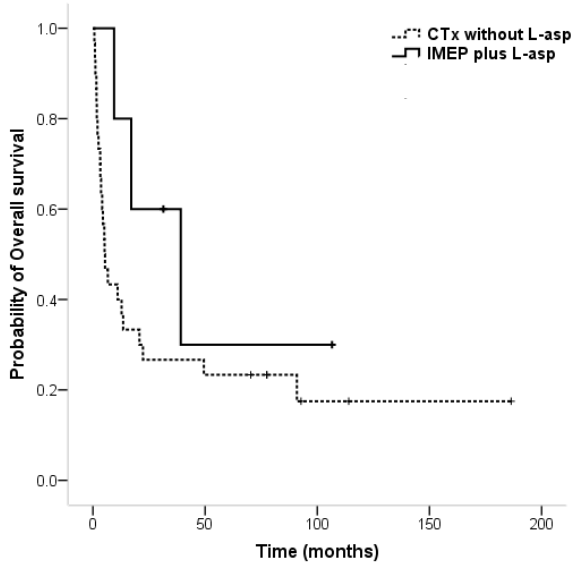
Although IMEP plus L-asp favorably affected OS and PFS in patients with UAT-NTCL (P = 0.004 and P < 0.001 respectively; Figures 2A-B), it did not significantly prolong survival in patients with NUAT-NTCL (P = 0.219 and P = 0.799, respectively; Figures 2C-D). In patients treated with chemotherapy without L-asp, there were no survival differences between the anthracycline-treated and IMEP-treated groups (median OS, 5.2 vs. 6.2 months, P = 0.229; median PFS, 3.2 vs. 3.2 months, P = 0.432).

Figure 2. Kaplan-Meier plots of (A) OS and (B) PFS of patients with UAT-NTCL and (C) OS and (D) PFS of patients with NUAT-NTCL according to the first-line chemotherapy

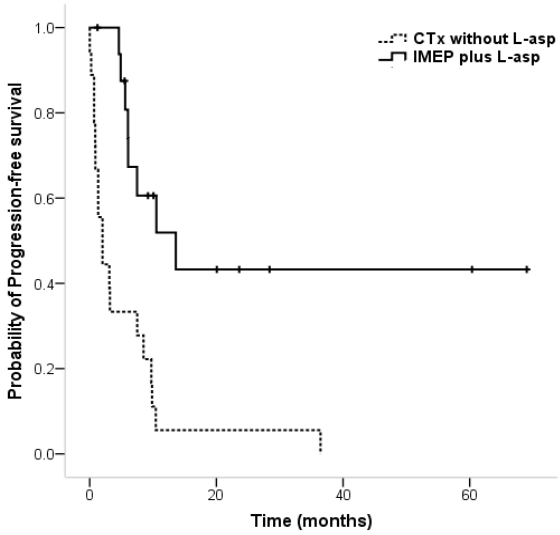
(A) Kaplan-Meier plots of OS of patients with UAT-NTCL according to the first-line chemotherapy



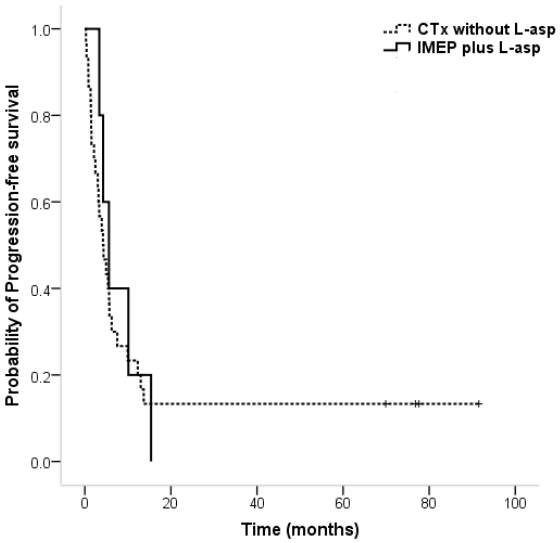
(B) Kaplan-Meier plots of OS of patients with NUAT-NTCL according to the first-line chemotherapy



(C) Kaplan-Meier plots of PFS of patients with UAT-NTCL according to the first-line chemotherapy



(D) Kaplan-Meier plots of PFS of patients with NUAT-NTCL according to the first-line chemotherapy



Prediction of Survivals

Regarding OS, significant factors by univariate analysis were elevated LDH level, poor ECOG PS, two or more extranodal sites, high IPI scores, and treatment with chemotherapy without L-asp. In multivariate analysis, independent factors adversely affecting OS were age > 60 years, poor performance status, two or more extranodal sites, and chemotherapy without L-asp (Table III).

Table 3. Predictors for OS using Cox regression analysis

Clinical factors	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age older than 60 years	1.72 (0.91-3.24)	0.095	2.02 (1.01-4.06)	0.047
NUAT presentation	0.97 (0.56-1.68)	0.905	-	-
Presence of B symptoms	1.22 (0.66-2.23)	0.526	-	-
Elevated LDH level	3.53 (1.27-9.80)	0.016	-	-
ECOG PS ≥ 2	2.16 (1.25-3.73)	0.006	1.96 (1.07-3.58)	0.029
Extranodal sites ≥ 2	2.18 (1.09-4.35)	0.028	2.36 (1.16-4.82)	0.018
IPI score 3-5	2.85 (1.28-6.34)	0.010	-	-
Chemotherapy without L-asp	2.48 (1.27-4.83)	0.008	2.18 (1.08-4.40)	0.030

Factors associated with PFS by univariate analysis were poor ECOG PS and use of chemotherapy without L-asp. Multivariate analysis confirmed that poor performance status and use of chemotherapy without L-asp were independent predictors for reduced PFS (Table IV). There were no significant factors associated with DFS in univariate or multivariate analyses (data not shown).

Table 4. Predictors for PFS using Cox regression analysis

Clinical factors	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age older than 60 years	1.37 (0.73-2.57)	0.323	-	-
NUAT presentation	1.27 (0.76-2.15)	0.364	-	-
Presence of B symptoms	1.41 (0.78-2.55)	0.255	-	-
Elevated LDH level	2.29 (0.98-5.36)	0.056	-	-
ECOG PS ≥ 2	2.37 (1.40-4.03)	0.001	2.10 (1.23-3.59)	0.007
Extranodal sites ≥ 2	1.23 (0.66-2.30)	0.509	-	-
IPI score 3-5	1.73 (0.87-3.43)	0.120	-	-
Chemotherapy without L-asp	2.56 (1.38-4.78)	0.003	2.29 (1.22-4.29)	0.010

DISCUSSION

Our study demonstrates that chemotherapy with IMEP plus L-asp as front-line treatment is active against stage III/IV NTCL. In addition, IMEP plus L-asp significantly improved survival in patients with advanced NTCL compared with chemotherapy without L-asp. Poor ECOG PS and chemotherapy without L-asp were independent factors for reduced OS and PFS.

Since the first case report of L-asp treatment in relapsed NTCL (16), several subsequent retrospective studies and a few phase II studies have shown that a L-asp-containing regimen resulted in ORR of 67-81% and CR rate of 45-66%, which represented a survival benefit in relapsed or refractory NTCL (Table V) (6-8, 17-19). These favorable results were comparable to those of patients with stage III/IV NTCL who were treated with IMEP plus L-asp in this study. However, heterogeneity in patient populations existed across most studies and patients with stage III/IV NTCL accounted for only 27-71% of the patient population. In contrast, all NTCL patients in our study were Ann Arbor stage III/IV, suggesting a

relatively homogenous population. In addition, treatment outcomes were compared based on chemotherapeutic regimens, and there were no differences in survival outcomes between CHOP-like and IMEP groups before the L-asp era. This indicated that CHOP-like regimens were unsatisfactory for the treatment of advanced NTCL, as shown in previous studies (20, 21).

IMEP, a non-anthracycline-based combination chemotherapy regimen, was moderately effective for relapsed or refractory NTCL as a second-line treatment and achieved an ORR of 44% (22). In addition, front-line IMEP resulted in ORR of 73% (CR rate, 27%) with favorable safety profiles in stage I/II NTCL in a prospective multicenter trial (23). Therefore, IMEP is active and safe for patients with NTCL and was commonly used in combination with and without L-asp in this study. Although febrile neutropenia was observed in 41% of patients treated with IMEP plus L-asp in our study, there were no treatment-related deaths. Considering that 5-7% of patients treated with the SMILE regimen experience treatment-related deaths (6, 7). IMEP plus L-asp might be a reasonable option for the treatment of advanced NTCL. Due to the significant toxicities of

the SMILE regimen, a modified SMILE regimen was retrospectively investigated in advanced or relapsed/refractory NTCL (24) and showed efficacy similar to that of other L-asp based regimens. Although CR, ORR, and PFS in the modified SMILE group were superior to those in the CHOP group, modified SMILE showed only a trend towards improved OS (24). Similarly, front-line IMEP plus L-asp significantly improved treatment outcomes in stage III/IV NTCL compared with CHOP-like regimens in our study. However, IMEP plus L-asp did not seem to be beneficial to our patients with stage III/IV NUAT-NTCL, and other active combination chemotherapy regimens should be investigated in this subset. Because NUAT-NTCL is a unique subset and is heterogeneous in terms of clinical prognostic factors and survival outcomes (11), treatment strategies might be explored separately from UAT-NTCL.

Poor ECOG PS adversely affected the OS of NTCL and was an independent predictor for reduced OS of UAT-NTCL in the largest Korean survey (11). ECOG PS was an independent factor for DFS in relapsed or refractory NTCL in the Asia Lymphoma Study Group (6). In addition, ECOG PS 1-2 was

associated with reduced OS in a univariate analysis by the NK-Cell Tumor Study Group (7). Similarly, ECOG PS ≥ 2 was an independent factor for reduced OS and PFS of stage III/IV NTCL in our study. Because patients who were treated with chemotherapy without L-asp had more NUAT presentations and a worse ECOG PS than those treated with IMEP plus L-asp, these factors might compromise survival outcomes in this group. The involvement of two or more extranodal sites was an independent predictor for reduced OS in NUAT-NTCL (11), as in our analysis for OS in stage III/IV NTCL.

In conclusion, IMEP plus L-asp is an independent predictor for improved survival in patients with Ann Arbor stage III/IV NTCL. In addition, this regimen was well tolerated without treatment-related deaths and showed comparable outcomes to other L-asp containing regimens, including SMILE. However, IMEP plus L-asp should be prospectively evaluated in NTCL and new treatment strategies should be investigated, especially in NUAT-NTCL. Taken together, our data indicate that L-asp containing regimens might be useful as a first-line treatment for stage III/IV NTCL.

Table 5. Recent studies of L-asparaginase-based chemotherapy for NTCL

	Present study	The NK-Cell Tumor Study Group (7)	The Asia Lymphoma Study Group(6)	GELA and GOELAMS intergroup (8)	Beiijing Cancer Hospital (18)	French study (19)
Regimen	IMEP + L-asp	SMILE	SMILE	AspaMetDex	Vincristine + Dex + L-asp	L-asp -based regimen
No. of patients	22	38	87	19	45	15
Study period	2000-2013	2007-2009	2005-2012	2006-2008	1996-2008	2003-2006
Disease Status	Newly- diagnosed stage III/IV	Newly- diagnosed stage IV, Refractory/ relapsed	Newly- diagnosed, Refractory/ relapsed	Refractory/ relapsed	Refractory/ relapsed	Refractory/ relapsed, Stage IV
UAT / NUAT	17(77.3)/5(22.7)	35(92%)/3(8%)	60(69%)/21(24%) Disseminated 6(7%)	- / -	39(87%)/6(13%)	10(75%)/5(25%)
AAB stage I-II / III-IV	- /22(100%)	11(29%)/27(71%)	38(43%)/49(56%)	12(63%)/7(27%)	33(73%)/12(27%)	5(33%)/10(66%)
ORR	90%	79% (after 2cycles)	81%	77.8%	66.9%	-
CR rate	65%	45%	66%	61%	55.6%	58.3%
PFS	43.3% (1-year)	53% (1-year)	64% (5-year DFS)	-	-	-
OS	75.6% (1-year)	55% (1-year)	50% (5-year)	Median 12.2months	66.9% (5-year)	-

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국문 초록

서론: III/IV 기 NK/T 세포 림프종 환자들의 예후는 매우 불량하다고 알려져 있다. 이러한 NK/T 세포 림프종의 치료에 있어서 L-asparaginase 가 효과적이라고 알려져 있지만, 그 중요성이 분명하게 입증되지 않았을 뿐만 아니라, 현재까지 III/IV 기 NK/T 세포 림프종의 치료 성적을 비교한 연구는 드문 편이다. 본 연구 III/IV 기 NK/T 세포 림프종에서 L-asparaginase 근간의 복합항암화학요법의 치료 효과와 예후 인자를 평가하고자 한다.

대상 및 방법: 2000 년 1 월부터 2013 년 2 월까지 총 70 명의 새롭게 진단된 III/IV 기 NK/T 세포 림프종 환자가 본 연구에 포함되었다. 모든 환자는 초치료로서 IMEP 및 L-asparaginase 의 복합항암화학요법 (22 명) 또는 L-asparaginase 가 포함되지 않은 복합항암화학요법 (48 명)을 시행받았다. 두 집단간의 임상적 예후 인자, 치료 성적 및 예후 점수를 비교하였다.

결과: 12.8 개월의 중앙 추적 관찰 기간 (범위 1.1-186.6 개월) 후, 중앙 전체 생존 기간 및 무진행 생존 기간은 각각 11.3 개월 과 5.6 개월이었다. L-asparaginase 가 포함되지 않은 복합항암화학요법으로 치료를 환자들에 비해 IMEP 및 L-

asparaginase 로 치료 받은 환자들에서 더 높은 반응률과 관해율을 보였다 (반응률, 90.0% 대 34.8, P < 0.001; 관해율, 65.0% 대 21.7%, P = 0.001). 전체 생존 및 무진행 생존은 L-asparaginase 가 포함되지 않은 복합항암화학요법으로 치료를 환자들에 비해 IMEP 및 L-asparaginase 로 치료받은 환자에서 유의하게 높았다. 다변량 분석에 L-asparaginase 가 포함되지 않은 복합항암화학요법의 사용이 전체 생존 및 무진행 생존 감소의 독립적인 예측인자임을 확인하였다 (위험비=2.18, 95 % 신뢰 구간 1.08-4.40, P = 0.030, 위험비=2.29, 95 % 신뢰 구간 1.22-4.29, P = 0.010).

결론: IMEP 및 L-asparaginase 복합항암화학요법은 III/ IV 기 NK/T 세포 림프종에 효과적이며, 생존률 향상의 독립적인 예측인자이다.

주요어 : ifosfamide, methotrexate, etoposide, prednisolone, L-asparaginase, NK/T 세포 림프종

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