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ORIGINAL ARTICLE

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

Miso Kim · Tae Min Kim · Ki Hwan Kim · Bhumsuk Keam · Se-Hoon Lee · Dong-Wan Kim · Jong Seok Lee · Yoon Kyung Jeon · Chul Woo Kim · Dae Seog Heo

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Abstract 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. 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. 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 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, the use of chemotherapy without L-asp was an independent predictor of 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). IMEP plus L-asp is active against stage III/IV NTCL, and it is an independent predictor of improved survival.

Keywords Ifosfamide · Methotrexate · Etoposide · Prednisolone · L-asparaginase · Extranodal NK/T-cell lymphoma, nasal type

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M. Kim · T. M. Kim (✉) · B. Keam · S.-H. Lee · D.-W. Kim · D. S. Heo
Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, 101 Daehak-roJongno-gu Seoul 110-744, South Korea
e-mail: gabriel9@snu.ac.kr

K. H. Kim
Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, South Korea

J. S. Lee
Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea

Y. K. Jeon · C. W. Kim
Department of Pathology, Seoul National University Hospital, Seoul, South Korea

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 an 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 [1, 9]; (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 data were collected including 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 [10]. 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 [11]. This outcome research using human subjects 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. Although selection of chemotherapy regimens was at the discretion of the physicians, IMEP plus L-asp was mainly used since 2007. Treatment was planned up to six to eight cycles and given until disease progression, unacceptable toxicities, or patient's refusal. Eight and four patients received sequential radiotherapy and stem cell transplantation at relapse, respectively.

The conventional IMEP regimen consists of ifosfamide at a dose of 1.5 g/m^2 intravenously on days 1 to 3 with adequate hydration of 2 l of half-saline per day and mesna to prevent hemorrhagic cystitis, methotrexate at a dose of 30 mg/m^2 intravenously on days on 3 and 10, etoposide at a dose of 100 mg/m^2 intravenously on days 1 to 3, and prednisolone at a dose of 60 mg/m^2 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/m^2 on days 4, 6, 8, 11, 13, and 15 before January 2010 (N=7) and modified IMEP plus L-asp (methotrexate 30 mg/m^2 on day 4 and L-asp 6,000 IU/m^2 on days 1, 3, 5, 7, 9, and 11 after January 2010; N=15).

Clinical responses were assessed by physical and otolaryngologic examinations and CT scans using the response criteria for lymphoma [12]. Adverse events could be assessed in patients treated with IMEP plus L-asp during admission or at the nadir according to 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 [13]. 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 [14]. 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, NY, USA).

Results

Patients' characteristics

Patients' characteristics are summarized in Table 1. 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.

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 overall response rate (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 2). 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 %).

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, 5.6, 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 2, Fig. 1a, b). The IMEP plus L-asp group showed a tendency toward prolonged DFS (Fig. 1c). Although IMEP plus L-asp favorably affected OS and PFS in patients with UAT-NTCL ($P=0.004$ and $P<0.001$, respectively; Fig. 2a, b), it did not significantly prolong survival in patients with NUAT-NTCL ($P=0.219$ and $P=0.799$, respectively; data not shown). Regarding IPI risk groups, IMEP plus L-asp significantly prolonged OS and PFS in the high IPI risk group (3 to 5) ($P=0.007$ and $P<0.001$, respectively). However, it did not prolong survivals in the low IPI risk group (0 to 2) ($P=0.826$ for OS and $P=0.990$ for PFS). In patients treated with chemotherapy without L-asp,

Table 1 Patient characteristics

Characteristics	No. of patients (%)
Age	
≤60 years	55 (78.6)
>60 years	15 (21.4)
Presentation	
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)
Involved sites other than UAT	
Bone marrow	25 (35.7)
Skin	16 (22.9)
Distant lymph nodes	15 (21.4)
Soft tissues	9 (12.9)
Gastrointestinal tract	7 (10.0)
IPI scores	
0–1	4 (5.7)
2	12 (17.1)
3	26 (34.1)
4–5	28 (40.0)

UAT upper aerodigestive tract, *NUAT* non-upper aerodigestive tract, *LDH* lactate dehydrogenase, *ECOG* Eastern Cooperative Oncology Group, *IPI* international prognostic index

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
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
Presentation	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 3–5	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

UAT upper aerodigestive tract, *NUAT* non-upper aerodigestive tract, *IMEP* etoposide, ifosfamide, methotrexate, and prednisolone, *LDH* lactate dehydrogenase, *ECOG* Eastern Cooperative Oncology Group, *IPI* international prognostic index, *CR* complete remission, *OS* overall survival, *PFS* progression-free survival, *DFS* disease-free survival

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).

Prediction of survival

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 3).

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

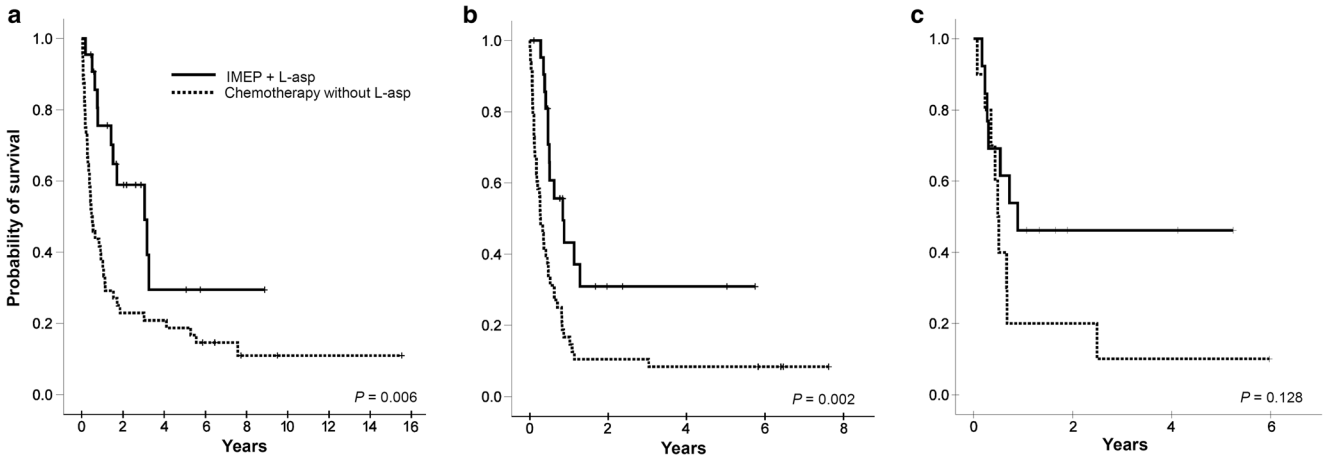

Fig. 1 Kaplan–Meier plots of **a** OS, **b** PFS, and **c** DFS of all NTCL patients according to the first-line chemotherapy

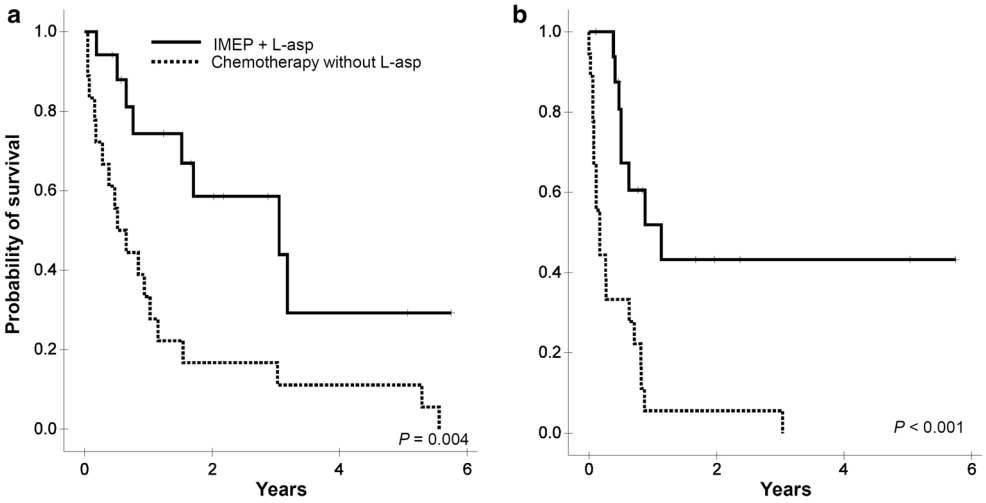

Fig. 2 Kaplan–Meier plots of **a** OS and **b** PFS of patients with UAT-NTCL according to the first-line chemotherapy

predictors of reduced PFS (Table 3). There were no significant factors associated with DFS in univariate or multivariate analyses (data not shown).

Discussion

Our study demonstrates that chemotherapy with IMEP plus L-asp as frontline 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 [15], several subsequent retrospective studies and a few phase II studies have shown that an 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 4) [6–8, 16–18]. 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 [19, 20].

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 % [21]. In addition, frontline IMEP resulted in an ORR of 73 % (CR rate, 27 %) with favorable safety profiles in stage

Table 3 Predictors of OS and PFS using Cox regression analysis

Clinical factors	Overall survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Age older than 60 years	1.72 (0.91–3.24)	0.095	2.02 (1.01–4.06)	0.047	1.37 (0.73–2.57)	0.323	–	–
NUAT presentation	0.97 (0.56–1.68)	0.905	–	–	1.27 (0.76–2.15)	0.364	–	–
Presence of B symptoms	1.22 (0.66–2.23)	0.526	–	–	1.41 (0.78–2.55)	0.255	–	–
Elevated LDH level	3.53 (1.27–9.80)	0.016	–	–	2.29 (0.98–5.36)	0.056	–	–
ECOG PS ≥2	2.16 (1.25–3.73)	0.006	1.96 (1.07–3.58)	0.029	2.37 (1.40–4.03)	0.001	2.10 (1.23–3.59)	0.007
Extranodal sites ≥2	2.18 (1.09–4.35)	0.028	2.36 (1.16–4.82)	0.018	1.23 (0.66–2.30)	0.509	–	–
IPI score 3–5	2.85 (1.28–6.34)	0.010	–	–	1.73 (0.87–3.43)	0.120	–	–
Chemotherapy without L-asp	2.48 (1.27–4.83)	0.008	2.18 (1.08–4.40)	0.030	2.56 (1.38–4.78)	0.003	2.29 (1.22–4.29)	0.010

NUAT non-upper aerodigestive tract, *ECOG* Eastern Cooperative Oncology Group, *LDH* lactate dehydrogenase, *IPI* international prognostic index, *HR* hazard ratio, *CI* confidence interval

Table 4 Recent studies of L-asp–based chemotherapy for NTCL

	Present study	The NK-Cell Tumor Study Group [7]	The Asia Lymphoma Study Group [6]	GELA and GOELAMS intergroup [8]	Beijing Cancer Hospital [17]	French study [18]
Regimen	IMEP+L-asp	SMILE	SMILE	L-aspMetDex	Vincristine+ Dex+L-asp	L-asp-based regimen
No. of patients	22	38	87	19	45	15
Study nature	Retrospective	Prospective phase II	Prospective phase I/II	Prospective phase II	Retrospective	Retrospective
Disease status	Newly diagnosed stage III/IV	Newly diagnosed stage IV, refractory/relapsed	Newly diagnosed, refractory/relapsed (any stage)	Refractory/relapsed	Refractory/relapsed	Refractory/relapsed, stage IV
UAT	17 (77.3)	35 (92 %)	60 (69 %)	–	39 (86.7 %)	10 (75 %)
NUAT	5 (22.7)	3 (8 %)	21 (24 %) Disseminated 6 (7 %)	–	6 (13.3 %)	5 (25 %)
Stage						
I–II	–	11 (29 %)	38 (43 %)	12 (63 %)	33 (73.3 %)	5 (33 %)
III–IV	22 (100 %)	27 (71 %)	49 (56 %)	7 (27 %)	12 (26.7 %)	10 (66 %)
ORR	90 %	79 % (after 2 cycles)	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, 12.2 months	66.9 % (5-year)	–

IMEP etoposide, ifosfamide, methotrexate, and prednisolone, *SMILE*, dexamethasone, methotrexate, ifosfamide, L-asp, and etoposide, *Met* methotrexate, *Dex* dexamethasone, *UAT* upper aerodigestive tract, *NUAT* non-upper aerodigestive tract, *ORR* overall response rate, *CR* complete remission, *DFS* disease-free survival, *PFS* progression-free survival, *OS* overall survival

I/II NTCL in a prospective multicenter trial [22]. 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. Therefore, IMEP plus L-asp might be a reasonable option for the treatment of advanced NTCL. Due to the significant toxicities of the dexamethasone, methotrexate, ifosfamide, L-asp, and etoposide (SMILE) regimen, a modified SMILE regimen was retrospectively investigated in advanced or relapsed/refractory NTCL [23] 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 toward improved OS [23]. Similarly, frontline 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 those with low IPI scores, and other active combination chemotherapy regimens should be investigated in these groups. Because NUAT-NTCL is a unique subset and is heterogeneous in terms of clinical prognostic factors and survival outcomes [10], treatment strategies might be explored separately from UAT-NTCL. However, because only five patients with NUAT-NTCL received IMEP plus L-asp and a wide array of chemotherapy regimens was given, it is cautious to compare the outcomes of IMEP plus L-asp with those of chemotherapy without L-asp in NTCL. In addition, changes in diagnostic criteria [1, 9], staging and re-staging [12, 24], and treatment strategy during the time lag between January 2000 and February 2013 should be taken into consideration to interpret our results.

Poor ECOG PS adversely affected the OS of NTCL and was an independent predictor of reduced OS of UAT-NTCL in the largest Korean survey [10]. 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 introduce a bias in interpreting the results and compromise survival outcomes in this group. The involvement of two or more extranodal sites was an independent predictor of reduced OS in NUAT-NTCL [10], as in our analysis for OS in stage III/IV NTCL.

In conclusion, IMEP plus L-asp is an independent predictor of 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 including the optimizing use of L-asp based on asparaginase activity [25] or antiasparaginase antibody [8] and alternative use of *Erwinia* asparaginase in case of hypersensitivity might 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.

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Conflict of interest The authors declare that they have no conflict of interest.

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