Overview

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Title: A Phase II Study of Ifosfamide, Methotrexate, Etoposide, and Prednisolone for Previously Untreated Stage I/II Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type: A Multicenter Trial of the Korean Cancer Study Group

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Author Summary: Abstract and Brief Discussion

Background
Combination chemotherapy consisting of ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) was active as first-line and second-line treatment for extranodal natural killer/T-cell lymphoma (NTCL).

Methods
Forty-four patients with chemo-naïve stage I/II NTCL were enrolled in a prospective, multicenter, phase II study and received six cycles of IMEP (ifosfamide 1.5 g/m^2 on days 1–3; methotrextate 30 mg/m^2 on days 3 and 10; etoposide 100 mg/m^2 on days 1–3; and prednisolone 60 mg/m^2 per day on days 1–5) followed by involved field radiotherapy (IFRT).

Results
Overall response rates were 73% (complete remission [CR] in 11 of 41 evaluable patients [27%]) after IMEP chemotherapy and 78% (CR 18 of 27 evaluable patients [67%]) after IMEP followed by IFRT. Neutropenia and thrombocytopenia were documented in 33 patients (75%) and 7 patients (16%), respectively. Only 8 patients (18%) experienced febrile neutropenia. Three-year progression-free survival (PFS) and overall survival (OS) were 66% and 56%, respectively. High Ki-67 ($\geq$70%) and Ann Arbor stage II independently reduced PFS ($p = .004$) and OS ($p = .001$), respectively.

Conclusion

Due to the high rate of progression during IMEP chemotherapy, IFRT needs to be introduced earlier. Moreover, active chemotherapy including an L-asparaginase-based regimen should be use to reduce systemic treatment failure in stage I/II NTCL.

Discussion

Our trial was based on the scheme of chemotherapy followed by radiotherapy (sequential). However, other trials used concurrent chemoradiation followed by ifosfamide plus etoposide-based combination chemotherapy [4, 5]. Although the designs of two concurrent chemoradiation trials [4, 5] were very similar, large differences were observed regarding survival data. We chose the JCOG0211 study [4] for comparison with our data because the other study provided limited information on patterns of failure due to short-term follow-up [5]. Our study showed a relatively higher locoregional failure rate (18% vs. 4%) but lower rates of systemic failure than in the JCOG0211 study (14% vs. 33%). These data suggest that upfront chemoradiation is favorable for locoregional control, but it is unfavorable for systemic failure in stage I/II natural killer/T-cell lymphoma (NTCL). Extended chemotherapy of up to six cycles in our study might be a factor for the high incidence of locoregional failure. Better coordination of the sequence between chemotherapy and radiotherapy might reduce both locoregional and systemic failures. A reduced number of cycles of chemotherapy, for example, followed by involved field radiotherapy (IFRT), concurrent chemoradiation, or sandwich radiotherapy during chemotherapy may be more efficacious for untreated stage I/II NTCL. Considering that the planned doses were reduced for 11 patients (25%) in 35 of 229 cycles (15%) in our study, the ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) regimen was safe and relatively well tolerated.

Recently, regimens based on L-asparaginase (L-asp) have shown promising efficacy in patients with refractory/relapsed or newly diagnosed advanced NTCL (overall response rate of 78%–81% and complete response [CR] of 45%–66%) [6–8] and with untreated stage I/II NTCL (CR of 90%, 2-year overall survival [OS] of 88%, and 2-year progress-free survival [PFS] of 90%) [10]. Furthermore, gemcitabine, which is active against NTCL [11], plus oxaliplatin and L-asp followed by IFRT resulted in a CR rate of 74% and 2-year PFS of 86% in stage I/II upper aerodigestive tract NTCL [12]. Furthermore, sandwich L-asp, vincristine, and prednisolone chemotherapy with IFRT showed a promising outcome (2-year OS of 88.5% and 2-year PFS of 80.6%) [13]. Consequently, more active L-asp-based regimens should be introduced in patients with stage I/II NTCL.

The IMEP regimen is effective and safe in patients with stage I/II NTCL before the introduction of L-asp, and IMEP followed by IFRT resulted in improved treatment outcomes in localized NTCL (Table 1). However, a short-course of the L-asp-based regimen followed by IFRT or concurrent or sandwich radiation with an L-asp-based regimen should be introduced in patients with untreated stage I/II NTCL.

Trial Information

Disease	Lymphoma – Non-Hodgkin
Stage of disease / treatment	Primary
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Overall Response Rate
Secondary Endpoint	Complete response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall Survival
Additional Details of Endpoints or Study Design	Toxicities
Investigator's Analysis	Active but results overtaken by other developments

Drug Information

Drug 1 **Generic/Working name**	Ifosfamide
Drug class	Alkylating agent
Dose	1.5 g/m^2
Route	IV

Schedule of Administration	Days 1–3
Drug 2 **Generic/Working name**	Methotrexate
Drug class	Antimetabolite
Dose	30 g/m^2
Route	IV
Schedule of Administration	Days on 3 and 10
Drug 3 **Generic/Working name**	Etoposide
Drug class	Topoisomerase II
Dose	100 g/m^2
Route	IV
Schedule of Administration	Days 1–3
Drug 4 **Generic/Working name**	Prednisolone
Drug class	Other
Dose	60 g/m^2
Route	Oral (po)
Schedule of Administration	Days 1–5

Patient Characteristics

Number of patients, male	29
Number of patients, female	15
Stage	Ann Arbor stage I/II
Age	Median (range): 56 years (range, 21–70 years)
Number of prior systemic therapies	Median (range): 0
Performance Status:	ECOG 0 — 15 1 — 28 2 — 1 3 — unknown —
Other	Not Collected
Cancer Types or Histologic Subtypes	

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened:	48
Number of patients enrolled:	44
Number of patients evaluable for toxicity:	44
Number of patients evaluated for efficacy:	41
Evaluation method:	Other
Response assessment CR:	26%
Response assessment PR:	47%
Response assessment SD:	18%
Response assessment PD:	9%
Response assessment other:	0%
(Median) duration assessments PFS:	66%
(Median) duration assessments OS:	56%

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
Hemoglobin	7%	43%	29%	16%	5%	0%	93%
Leukocytes (total WBC)	7%	14%	23%	36%	20%	0%	93%
Neutrophils/granulocytes (ANC/AGC)	11%	2%	12%	30%	45%	0%	89%
Platelets	57%	18%	9%	5%	11%	0%	43%
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC ＜1.0 × 10e9/L, fever ≥38.5°C)	82%	0%	0%	18%	0%	0%	18%
Nausea	27%	68%	5%	0%	0%	0%	73%
Vomiting	84%	14%	2%	0%	0%	0%	16%
Mucositis/stomatitis (clinical exam)	61%	30%	9%	0%	0%	0%	39%
Diarrhea	89%	11%	0%	0%	0%	0%	11%
Constipation	64%	34%	2%	0%	0%	0%	36%
Neuropathy: sensory	91%	7%	2%	0%	0%	0%	9%
Bilirubin (hyperbilirubinemia)	82%	7%	9%	2%	0%	0%	18%
Creatinine	95%	5%	0%	0%	0%	0%	5%

*No Change from Baseline/No Adverse Event

Pharmacokinetics/Pharmacodynamics

N:	13
Cmax:	Not collected
AUC:	Not collected
Half-life:	Not collected
Volume of distribution:	Not collected
Clearance:	Not collected
Notes:	Bone marrow Epstein-Barr virus was positive in 4 of 13 patients (31%).

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Active but results overtaken by other developments

Discussion

A nationwide survey of the Korean Cancer Study Group revealed the clinical heterogeneity of natural killer/T-cell lymphoma (NTCL) and revealed two subsets based on clinical presentation: upper aerodigestive tract (UAT) and non-UAT NTCLs [1]. Nearly 90% of patients showed UAT presentation at Ann Arbor stage I/II NTCL, and 2-year overall survival (OS) and progress-free survival (PFS) were 60% and 45%, respectively. Systemic failure was observed in 25% of stage I/II NTCL patients treated with radiotherapy alone [2]. Combined chemotherapy and radiotherapy has been administered to improve treatment outcomes in localized NTCL [1, 3].

Like other recent clinical trials, our trial was based on etoposide-based combination chemotherapy because of poor outcomes observed with anthracycline-based combination chemotherapy. One of the key issues determined was the timing of radiotherapy. Our trial was based on the scheme of chemotherapy followed by radiotherapy (sequential). However, other trials used concurrent chemoradiation followed by ifosfamide plus etoposide-based combination chemotherapy [4, 5]. Although the designs of two concurrent chemoradiation trials [4, 5] were very similar, large differences were observed regarding survival data. We chose the JCOG0211 study [4] for comparison with our data because the other study provided limited information on patterns of failure due to short-term follow-up [5]. Our study showed a relatively higher locoregional failure rate (18% vs. 4%) but lower rates of systemic failure than in the JCOG0211 study (14% vs. 33%). These data suggest that upfront chemoradiation is favorable for locoregional control, but it is unfavorable for systemic failure in stage I/II NTCL.

Extended chemotherapy of up to six cycles in our study might be a factor for the high incidence of locoregional failure. Better coordination of the sequence between chemotherapy and radiotherapy might reduce both locoregional and systemic failures. A reduced number of cycles of chemotherapy, for example, followed by involved field radiotherapy (IFRT), concurrent chemoradiation, or sandwich radiotherapy during chemotherapy may be more efficacious for untreated stage I/II NTCL. Considering that the planned doses were reduced for 11 patients (25%) in 35 of 229 cycles (15%) in our study, the ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) regimen was safe and relatively well tolerated.

A wide variety of survival outcomes are possible in stage I/II NTCL, probably because of the heterogeneity of the patient population. Systemic symptoms were more frequently observed in our patients (75%) than in other studies (37%) [4, 5]. In addition, despite the low number of patients tested for bone marrow Epstein-Barr virus (EBV) status, detection of nuclear EBV oligonucleotide in bone marrow was observed in 31% of our patients and might be associated with advanced disease and high early failure rates and thus a rapid drop in the 1-year survival curve. This early drop (within 1 year) in the survival curve was also observed in JCOG0211 patients who did not achieve complete response (CR) after concurrent chemoradiation [4].

Recently, regimens based on L-asparaginase (L-asp) have shown promising efficacy (overall response rate of 78%–81% and CR of 45%–66%) in refractory/relapsed or newly diagnosed advanced NTCL [6–8]. In addition, IMEP plus L-asp showed similar outcomes with favorable safety profiles, like other L-asp-based regimens, and significantly improved survival in untreated stage III/IV NTCL compared with chemotherapy without L-asp [9]. Similarly, a high CR rate and excellent survival outcomes (CR of 90%, 2-year OS of 88%, and 2-year PFS of 90%) were observed in patients with stage I/II NTCL treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus L-asp followed by IFRT [10]. Furthermore, gemcitabine, which is active against NTCL [11], plus oxaliplatin and L-asp (GELOX) followed by IFRT resulted in a CR rate of 74% and 2-year PFS of 86% in stage I/II UAT-NTCL [12]. Furthermore, sandwich L-asp, vincristine, and prednisolone (LVP) chemotherapy with IFRT showed a promising outcome (2-year OS of 88.5% and 2-year PFS of 80.6%) [13]. Due to the higher toxicities of the SMILE regimen (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase, and etoposide), less toxic regimens such as IMEP plus L-asp [9], dose-modified SMILE [14], GELOX [12], and LVP [13] might be ideal options before IFRT or concurrent or sandwich chemoradiation in patients with untreated stage I/II NTCL. Considering that almost all patients with early failure did not survive more than 1 year in this study, more active and less toxic L-asp-based regimens should be investigated further in patients with stage I/II NTCL.

A high Ki-67 index was predictive of reduced PFS in our study, in line with previous reports [3, 15]. In addition, Ann Arbor stage II was independently correlated with reduced OS in stage I/II NTCL, suggesting that regional lymphadenopathy might adversely affect survival [1]. EBV-positive bone marrow was demonstrated in 15.4% of patients with stage I/II NTCL and these patients had lower survival than patients whose bone marrow was EBV negative [16]. Similarly, 31% of our patients who were EBV positive in the bone marrow trended toward reduced OS; however, it is unknown whether EBV-encoded RNA1 is present in lymphoma cells or in bystander, nonlymphoma cells in these bone marrow samples. Consequently, we are cautious about including stage I/II NTCL patients with bone marrow EBV positivity in the analysis of prospective trials for localized NTCL.

In conclusion, the IMEP regimen is effective and safe in patients with stage I/II NTCL before the introduction of L-asp, and IMEP followed by IFRT resulted in improved treatment outcomes in localized NTCL. Considering the high efficacy of the L-asp-based regimen, a short course of the L-asp-based regimen followed by IFRT or concurrent or sandwich radiation with an L-asp-based regimen should be introduced in patients with untreated stage I/II NTCL. The rational selection of L-asp-based combination chemotherapy and a well-coordinated sequence of radiotherapy should be determined in a future trial.

Acknowledgments

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Figures and Tables

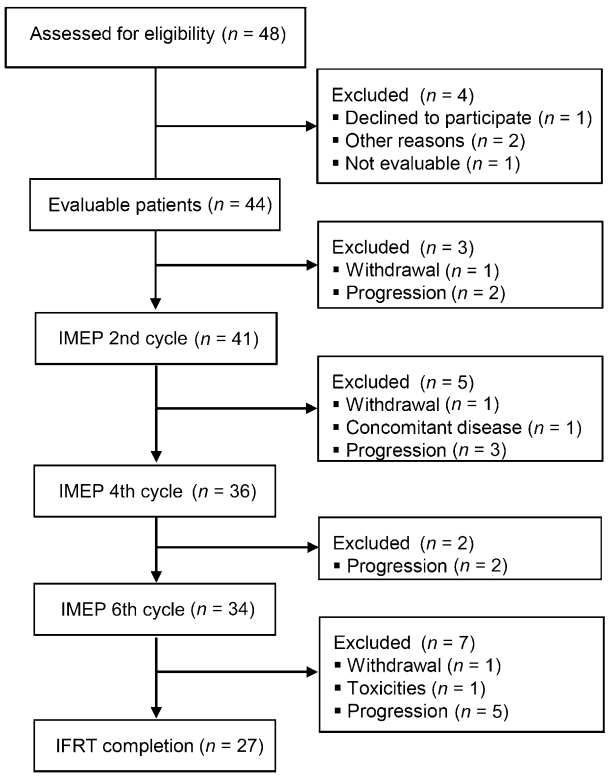

Figure 1. Flow diagram for eligible patients at each point of treatment.
Abbreviations: IFRT, involved field radiotherapy; IMEP, ifosfamide, methotrexate, etoposide, and prednisolone.

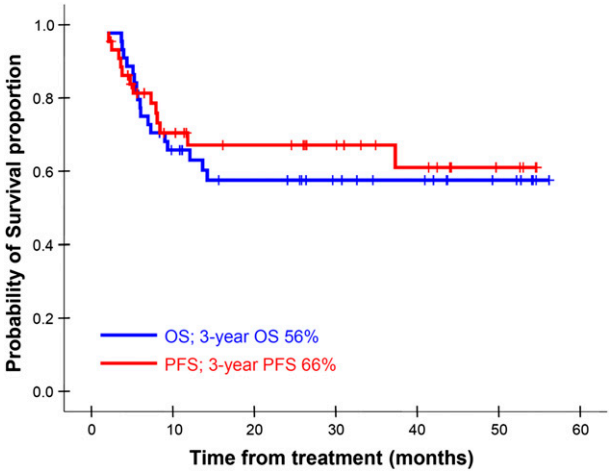

Figure 2. Kaplan-Meier plot for survival.
Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 1. Patient characteristics

Characteristic	*n*	%
Age		
≤60 years	31	70
>60 years	13	30
Presentations of tumor		
Nasal cavity	35	80
Nasopharynx	8	18
Oropharynx	3	7
Presence of B symptoms		
No	11	25
Yes	33	75
Ann Arbor stage		
IE	32	73
IIE	12	27
Performance status		
0	15	34
1	28	64
2	1	2
LDH level		
Normal	29	71
Elevated	12	29
Number of extranodal sites		
0–1	39	89
≥2	5	11
Tumor extent of involvements		
Single anatomic site	25	57
Spread to adjacent structures	15	34
Bony invasion with or without destruction	4	9
Ki-67 index		
<70%	26	68
≥70%	12	32

IPI score		
0	19	43
1	16	36
2	9	21
NK/T-cell lymphoma prognostic index		
1	3	7
2	22	54
3	15	37
4	1	2

Abbreviations: IPI, International Prognostic Index; LDH, lactate dehydrogenase; NK/T-cell, natural killer/T-cell.

Table 2. Treatment outcomes after completion of each treatment

Response	2nd cycle ($n = 41$)	4th cycle ($n = 36$)	6th cycle ($n = 34$)	IFRT ($n = 27$)
CR	7 (17)	9 (25)	9 (26)	18 (67)
PR	18 (44)	15 (42)	16 (47)	3 (11)
SD	14 (34)	9 (25)	6 (18)	2 (7)
PD	2 (5)	3 (8)	3 (9)	4 (15)
ORR, %	61	67	73	78

Data are shown as *n* (%) unless specified otherwise.
Abbreviations: CR, complete response; IFRT, involved field radiotherapy; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Patterns of failure

ID	Age, years/ sex	Local invasion	Stage	Treatments	Overall responses		Failures	Patterns	Failure sites	Survivals, months	
					IMEP	IFRT				PFS	OS
1	62/M	Adjacent	IB	IMEP4/IFRT	PR→PD	NE	Progression	Locoregional	Nasal cavity	2.83	7.30
2	39/M	Adjacent	IIA	IMEP6/IFRT	CR	PD	Relapse	Systemic	Lung	7.40	54.60
8	42/M	Single	IB	IMEP6/IFRT	PR	CR	Relapse	Locoregional	Nasal cavity	36.83	56.20
10	65/M	Single	IB	IMEP2	PD	NE	Progression	Locoregional	Nasal cavity	1.47	6.07
18	58/M	Adjacent	IIA	IMEP6/IFRT	PR	PD	Progression	Locoregional	Lymph node	7.90	12.10
21	52/F	Single	IB	IMEP2	PD	NE	Progression	Locoregional	Nasal cavity, nasopharynx	1.60	5.13
23	55/M	Bony	IA	IMEP6/IFRT	SD	PD	Progression	Locoregional Systemic	Nasal cavity, liver	6.80	6.97
28	64/F	Single	IB	IMEP6/IFRT	PR	CR	Relapse	Systemic	Breast, lymph node	11.30	13.67
29	31/M	Single	IB	IMEP6	CR→PD	NE	Progression	Systemic	Stomach	4.63	14.23
33	59/M	Single	IB	IMEP4	SD→PD	NE	Progression	Locoregional	Nasal cavity	3.23	9.03
34	49/M	Adjacent	IIA	IMEP1	PD	NE	Progression	Locoregional	Nasal cavity, nasopharynx	1.97	3.80
35	70/M	Single	IIB	IMEP6/IFRT	PR	PD	Progression	Locoregional	Lymph node	7.57	9.37
36	66/F	Bony	IIA	IMEP6	SD→PD	NE	Progression	Systemic	Spleen	4.23	5.57
41	46/F	Adjacent	IB	IMEP4	CR→PD	NE	Progression	Systemic	CSF, pleura, peritoneum	3.07	3.70

Abbreviations: CR, complete response; F, female; ID, patient identifier; IFRT, involved field radiotherapy; IMEP, ifosfamide, methotrexate, etoposide, and prednisolone; M, male; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progress-free survival; PR, partial response; SD, stable disease.

Table 4. Univariate and multivariate analyses for survivals

	PFS			OS		
Predictors	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**
Univariate analysis						
Ann Arbor stage	.125	2.5	0.8–7.7	.002	4.5	1.7–11.5
Lymphadenopathy	.208	2.1	0.7–6.6	.005	3.9	1.5–10.0
Elevated LDH level	.004	4.9	1.7–14.2	.032	2.8	1.1–7.1
Ki-67 ≥70%	.013	4.3	1.4–13.7	.172	2.1	0.7–6.1
Local invasiveness	.358	2.0	0.4–9.2	.095	2.9	0.8–10.2
Multivariate analysis						
Ann Arbor stage				.001	4.8	1.9–12.2
Ki-67 ≥70%	.004	5.6	1.8–17.6			

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

Table 5. Comparison of prospective phase II trials for stage I/II natural killer/T-cell lymphoma, nasal type

	No use of L-asp			Use of L-asp	
Characteristics	**Present study**	**DEVIC [4]**	**VIPD [5]**	**CHOP + L-asp [10]**	**GELOX [12]**
Patients, *n*	44	33	30	38 (7 stage III/IV)	27
Chemotherapy doses, schedules	I: 1.5 g/m^2, days 1–3; M: 30 mg/m^2, days 3, 10; E: 100 mg/m^2, days 1–3; P: 60 mg/m^2, days 1–5	D: 40 mg, days 1–3; E: 67 mg/m^2, days 1–3; I: 1.0 g/m^2, days 1–3; CARB: 200 mg/m^2, day 1	D: 40 mg, days 1–4; E: 100 mg/m^2, days 1–3; I: 1.2 g/m^2, days 1–3; CDDP: 33 mg/m^2, days 1–3	C: 750 mg/m^2, day 1; H: 50 mg/m^2, day 1; V: 1.4 mg/m^2, day 1; P: 10 mg, days 1–8; L-asp: 6,000 U/m^2, days 2–8	G: 1,000 mg/m^2, days 1–8; O: 130 mg/m^2, day 1; L-asp: 6,000 U/m^2, days 1–7
Planned cycles	6	3	3	6–8	6
Radiotherapy	Sequential	Upfront concurrent	Upfront concurrent	Sequential	Sequential
ORR/CR rates, *n* (%)	73 (27)	81 (77)	100 (73)	84.2 (81.6)	96.3 (74.1)
2-year OS, %	56	78	85	80.1	86
2-year PFS, %	66	67	86	81	86

Abbreviations: C, cyclophosphamide; CARB, carboplatin; CDDP, cisplatin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; D, dexamethasone; E, etoposide; G, gemcitabine; GELOX, gemcitabine plus oxaliplatin and L-asp; H, doxorubicin; I, ifosfamide; L-asp, L-asparaginase; M, methotrexate; O, oxaliplatin; ORR, overall response rate; OS, overall survival; P, prednisolone; PFS, progression-free survival; V, vincristine.

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