의학석사 학위논문

비형 extranodal NK/T-세포 림프종의 이차 중추신경계 침범의 임상양상과 위험인자 및 예후에 대한 연구

Clinical Presentation, Risk Factors, and Outcome of Secondary Central Nervous System Involvement of Extranodal NK/T-cell Lymphoma, Nasal Type

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의 학 과

정 혜 현

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이 논문을 의학석사 학위 논문으로 제출함

2020년 2 월

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Abstract

Introduction: Extranodal NK/T cell lymphoma, nasal type (ENKTL) is an uncommon, unique subset of non-Hodgkin lymphoma which frequently involves the nose and paranasal sinuses. Although secondary CNS relapse or progression of lymphoma is known to be associated with poor outcome, data on the secondary involvement of ENKTL are scarce. In this study, we analyzed clinical features and outcomes of secondary CNS involvement of ENKTL in the non-anthracycline-based treatment era.

Methods: Patients who had pathologically diagnosed ENKTL between 2003.1 and 2016.6 in Asan Medical Center, Seoul, Korea were included, excluding those with CNS involvement at diagnosis. CNS involvement was confirmed either by cytological examination of cerebrospinal fluid or imaging modalities such as MRI or CT of the affected sites. The Kaplan-Meier survival analysis was used to estimate the survival outcome, and Cox regression analysis was performed to identify possible risk factors for secondary CNS involvement of ENKTL.

Results: A total of 170 patients with ENKTL were included in this study. Out of the 170 patients, 109 patients (64.1%) were male. The median age at diagnosis was 52 years old (range: 16-83). The number of patients with stage I/II disease was 112 (65.9%) and stage III/IV was 58 (34.1%). The number of patients with low, intermediate, and high prognostic index of natural killer cell lymphoma (PINK) was 72 (42.4%), 38 (22.4%), and 60 (35.3%) respectively. For the first-line treatment, 33 patients (19.3%) received anthracycline-based chemotherapy, and 113 patients (66.5%) received non-anthracycline-based chemotherapy. During the 35.8 months of median follow-up, 9 patients (5.3%) developed secondary CNS

involvement. Among those 9 patients, 4 had leptomeningeal, 3 had brain parenchymal, and 2 had both leptomeningeal and brain parenchymal involvement. The median time from diagnosis to secondary CNS involvement of ENKTL was 5.0 months (95% confidence interval (CI), 4.6–5.3). The median overall survival (OS) after CNS involvement was 3.4 months (95% CI, 1.3–5.4). OS differed significantly between patients with and without secondary CNS involvement (with CNS involvement, 8.9 months (95% CI, 7.8–10.1) vs. without CNS involvement, 89.7 months (95% CI, 32.0–147.4), $P < 0.001$). After univariate Cox analysis, stage III/IV (hazard ratio (HR) 5.8 (95% CI, 1.5–23.4)), $P = 0.013$), lung or pleural involvement (HR 12.5 (95% CI, 3.3–47.5), $P < 0.001$), peritoneal involvement (HR 41.9 (95% CI, 7.4–236.9), $P = 0.001$), PINK $\geq$ 2 (HR 5.4 (95% CI, 1.4–21.9), $P = 0.017$), and first–line treatment with anthracycline–based chemotherapy (HR 4.8 (95% CI, 1.1–21.3), $P = 0.017$) showed association with secondary CNS involvement. Due to the small number of CNS events, multivariate analysis was not feasible. No statistically significant association was found with age, sex, serum lactate dehydrogenase level, > 1 extranodal sites involvement, high international prognostic index (IPI) or CNS–IPI, non–nasal ENKTL, and first–line regimens including high–dose methotrexate ($\geq$ 2g/m^2).

Conclusions: This study demonstrated that secondary CNS involvement of ENKTL in the non–anthracycline–based treatment era is still an uncommon, early event with a dismal outcome. For early detection, brain imaging or CSF analysis might be considered as a part of the initial diagnostic workup in high–risk patients.

Contents

List of Tables

List of Figures

Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKTL) is a rare subset of aggressive non-Hodgkin lymphoma with unique clinical features. It has higher prevalence in East Asia and Latin America [1-3], and typically presents as destructive facial mass involving nasal and paranasal area. Epstein-Barr virus (EBV) is known to be associated with its pathogenesis and prognosis [4,5]. A vast majority of cases have extranodal involvement at presentation as the disease has a predilection for midline facial structures. They may involve other extranodal sites such as the skin, liver, gastrointestinal tract, and the central nervous system (CNS). Among all the potential involved extranodal sites, CNS involvement of lymphoma has been an important issue because it can cause serious neurologic sequelae and related to poor survival outcome [6]. Moreover, it requires CNS-specific diagnostic methods and treatments, which need to be applied based on CNS relapse risk. For example, in the case of diffuse large B-cell lymphoma (DLBCL), there is a scoring system called "CNS-IPI" which stratifies patients according to CNS relapse risk. Although the overall incidence of CNS involvement in DLBCL is between 3-6% [7-9], there are huge differences in the CNS relapse rate among CNS-IPI risk groups, ranging from 0.6 to 12.0% and this helps physicians to decide which patients should be considered for CNS evaluation and prophylaxis.

However, literature regarding CNS involvement of ENKTL is scarce. A handful of data suggested the overall incidence of secondary CNS involvement of ENKTL falls between 3.7-5.8% [10,11], which is somewhat similar to that of DLBCL, but as there is no consensus on which patients are at higher risk of secondary CNS involvement current management strategy in ENKTL CNS relapse is largely based on small-sized data. Moreover,

previous study focused on the secondary CNS involvement of ENKTL [10] mainly included anthracycline-based chemotherapy-treated patients. This data may not be sufficient to support clinical decisions at this point, as there has been a major paradigm shift in the management of ENKTL recently. In the past, ENKTL patients typically received an anthracycline-based chemotherapy regimen, namely CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), but the tumor poorly responded to such treatment. During the past decade, non-anthracycline-based chemotherapy was introduced and brought major improvements in the outcome ENKTL. Therefore, new data regarding CNS relapse of ENKTL is required.

In this study, we analyzed clinical presentation, potential risk factors, and outcome of secondary CNS involvement of ENKTL who were mainly treated with non-anthracycline-based chemotherapy.

Methods

Patients who were pathologically diagnosed ENKTL in Asan medical center, Seoul, South Korea from January 2003 to August 2016 were identified for this study. As CNS imaging or spinal tapping were not part of the routine diagnostic tests throughout the study period, only patients who presented with neurologic symptoms underwent such examination. Among them, those who had CNS involvement at the initial diagnostic workup were excluded in the analysis. Clinical data such as baseline characteristics, treatment history, and survival outcomes were collected by reviewing the electronic medical records. The presence of CNS involvement of lymphoma was confirmed either by imaging modalities (CT or MRI of affected sites) or cytological examination of cerebrospinal fluid (CSF) samples. Secondary

CNS involvement of ENKTL is defined as newly noted evidence of CNS involvement of lymphoma which was not acknowledged at the time of the initial diagnosis, regardless of the presence of neurologic symptoms. The term “secondary CNS involvement” included both CNS relapse and progression. CNS relapse referred to secondary CNS involvement occurred during the patient was in complete remission (CR). If the patient had preexisting systemic lymphoma involvement when secondary CNS involvement occurred, it is considered as CNS progression. Time to secondary CNS involvement was defined as the period from the initial diagnosis of ENKTL to the confirmation of CNS relapse or progression. Overall survival (OS) after secondary CNS involvement was defined as the period from the date of CNS relapse or progression to the date of the patient’s death from any cause.

OS and time to secondary CNS involvement were estimated using the Kaplan–Meier method. Univariate analysis for evaluating risk factors associated with subsequent CNS involvement was performed by Cox regression. Multivariate analysis was not feasible due to the small sample size. A P–value of less than 0.05 was considered statistically significant. Statistical Package for the Social Sciences version 22.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

1. Baseline characteristics

A total of 176 patients were diagnosed with ENKTL from January 2003 to August 2016 in Asan Medical Center, Seoul, South Korea. Six patients with CNS involvement at the initial diagnosis were excluded. The median

follow-up duration was 35.8 months (interquartile range: 9.0-81.4 months). During the follow-up period, 9 out of 170 patients (5.3%) developed secondary CNS involvement.

The median age at diagnosis was 52 years old (range: 16-83). The number of patients treated with non-anthracycline-based chemotherapy and anthracycline-based chemotherapy was 113 (66.5%) and 33 (19.4%), respectively. In patients treated with non-anthracycline-based chemotherapy, VIDL (etoposide, ifosfamide, dexamethasone, L-asparaginase) was the most commonly used regimen (46 patients, 40.7%), followed by SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) (36 patients, 31.9%). The baseline characteristics of the patients are shown in table 1.

Table 1. Baseline patient characteristics

	Patients without CNS involvement (n=161)	Patients with CNS involvement (n=9)	Total (n=170)
Sex			
Male	106 (65.8%)	3 (33.3%)	109 (64.1%)
Female	55 (34.2%)	6 (66.7%)	61 (35.9%)
Age			
≤ 60	115 (71.4%)	5 (55.6%)	120 (70.6%)
> 60	46 (28.6%)	4 (44.4%)	50 (29.4%)
ECOG PS			
0-1	150 (93.2%)	8 (88.9%)	158 (92.9%)
2-4	11 (6.8%)	1 (11.1%)	12 (7.1%)
Stage			
I-II	109 (67.7%)	3 (33.3%)	112 (65.9%)
III-IV	52 (32.3%)	6 (66.7%)	58 (34.1%)
Number of extranodal sites involved			
≤ 1	109 (67.7%)	4 (44.4%)	113 (66.5%)
> 1	52 (32.3%)	5 (55.6%)	57 (33.5%)
Location			
Nasal	120 (74.5%)	5 (55.6%)	125 (73.5%)
Non-nasal	41 (25.5%)	4 (44.4%)	45 (26.5%)
Serum or blood EBV DNA at diagnosis			
Positive	72 (44.7%)	4 (44.4%)	76 (44.7%)
Negative	59 (36.6%)	2 (22.2%)	61 (35.9%)
Not done	30 (18.6%)	3 (33.3%)	33 (19.4%)

Table 1. (continued)

	Patients without CNS involvement (n=161)	Patients with CNS involvement (n=9)	Total (n=170)
Kidney/adrenal gland involvement at diagnosis			
No	150 (93.2%)	9 (100%)	159 (93.5%)
Yes	11 (6.8%)	0	11 (6.5%)
BM involvement at diagnosis			
No	139 (86.3%)	8 (88.9%)	147 (86.5%)
Yes	22 (13.7%)	1 (11.1%)	23 (13.5%)
Lung/pleural involvement at diagnosis			
No	146 (90.7%)	5 (55.6%)	151 (88.8%)
Yes	15 (9.3%)	4 (44.4%)	19 (11.2%)
Peritoneal involvement at diagnosis			
No	157 (97.5%)	7 (77.8%)	164 (96.5%)
Yes	4 (2.5%)	2 (22.2%)	6 (3.5%)
IPI			
Low	92 (57.1%)	4 (44.4%)	96 (57.8%)
Low-intermediate	26 (16.1%)	2 (22.2%)	28 (16.9%)
High-intermediate	22 (13.7%)	2 (22.2%)	24 (14.1%)
High	17 (10.6%)	1 (11.1%)	18 (10.6%)
Not evaluable	4 (2.5%)	0	4 (2.4%)
CNS-IPI			
Low	92 (57.1%)	4 (44.4%)	96 (56.5%)
Intermediate	41 (25.5%)	4 (44.4%)	45 (26.5%)
High	24 (14.9%)	1 (11.1%)	25 (14.7%)
Not evaluable	4 (2.5%)	0	4 (2.4%)

Table 1. (continued)

	Patients without CNS involvement (n=161)	Patients with CNS involvement (n=9)	Total (n=170)
PINK			
Low	70 (43.5%)	2 (22.2%)	72 (42.4%)
Intermediate	37 (23.0%)	1 (11.1%)	38 (22.4%)
High	54 (33.5%)	6 (66.7%)	60 (35.3%)
First-line treatment			
Anthracycline based	29 (18.0%)	4 (44.4%)	33 (19.4%)
Non-anthracycline based	110 (68.3%)	3 (33.3%)	113 (66.5%)
RT ± cisplatin	7 (4.3%)	2 (22.2%)	9 (5.3%)
Follow-up loss or not treated	15 (9.3%)	0	15 (8.8%)

CNS, central nervous system; ECOG PS, eastern cooperative oncology group performance status; EBV, Epstein-Barr virus; BM, bone marrow; IPI, international prognostic index; PINK, prognostic index of natural killer lymphoma; RT, radiotherapy.

2. Survival outcome

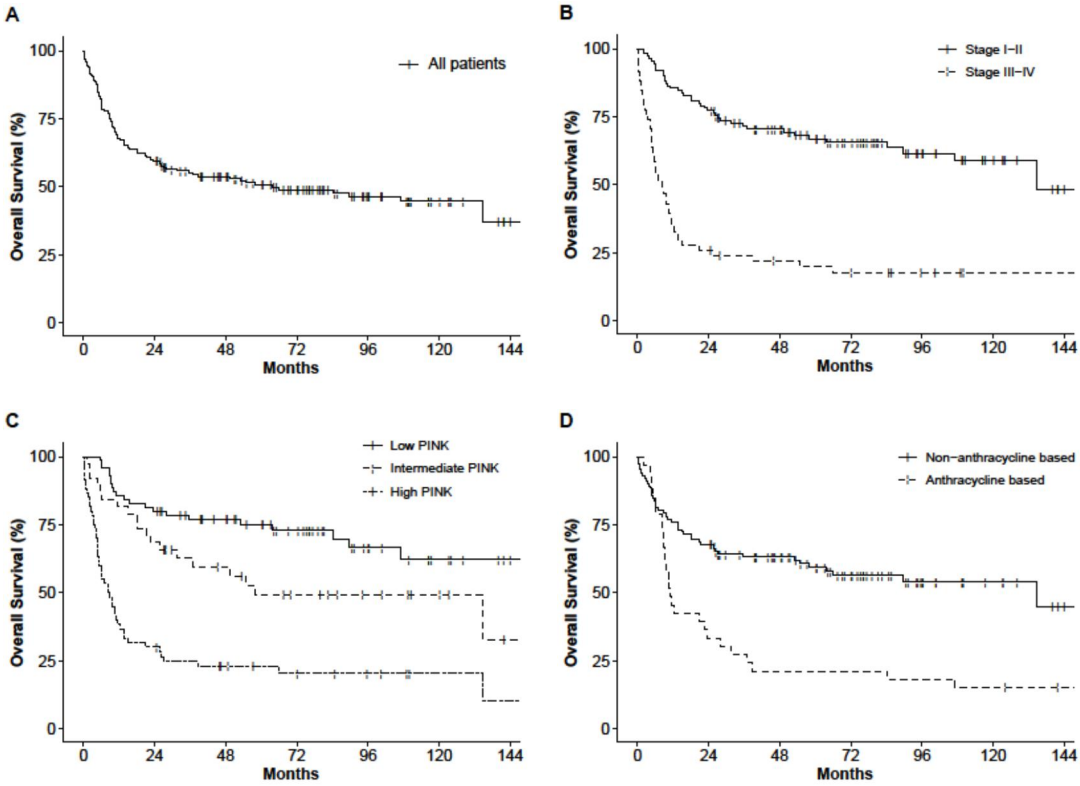

Fig 1. Overall survival by clinical characteristics.

(A) All patients. 63.5 months (95% CI, 10.2–116.9),

(B) By stage at diagnosis. Stage I–II = 134.9 months (95% CI, not estimated), stage III–IV = 8.3 months (95% CI, 4.1–12.6), P < 0.001,

(C) PINK score. Low = median not reached, intermediate = 58.0 months (95% CI, 0–119.8), high = 8.5 months (95% CI, 4.5–12.9), P < 0.001,

(D) First–line chemotherapy. Non–anthracycline–based = 134.9 months (95% CI, 24.9–244.8), anthracycline–based = 11.0 months (95% CI, 7.8–14.3), P < 0.001.

The median OS was 63.5 months (95% confidence interval (CI), 10.2–116.9). One, three, five–year survival after diagnosis was 67.9%, 55.1%,

and 50.6%, respectively. OS differed significantly according to disease stage, PINK (prognostic index of natural killer lymphoma) score at diagnosis, initial treatment regimen (anthracycline or non-anthracycline-based chemotherapy) (Figure 1). The five-year survival rates of patients with stage I-II disease and III-IV were 66.9% and 19.8%, respectively. The five-year survival rates of patients with low, intermediate, high PINK scores were 75.0%, 49.2%, 22.9%, respectively. Additionally, among those who had serum or blood Epstein-Barr virus DNA PCR result at diagnosis, patients who were EBV-positive (N=76) showed significantly shorter median OS than that of who were EBV-negative (N=61) (21.0 months (95% CI, 5.6-36.3) vs median not reached, P < 0.001)

3. Clinical characteristics and patterns of secondary CNS involvement

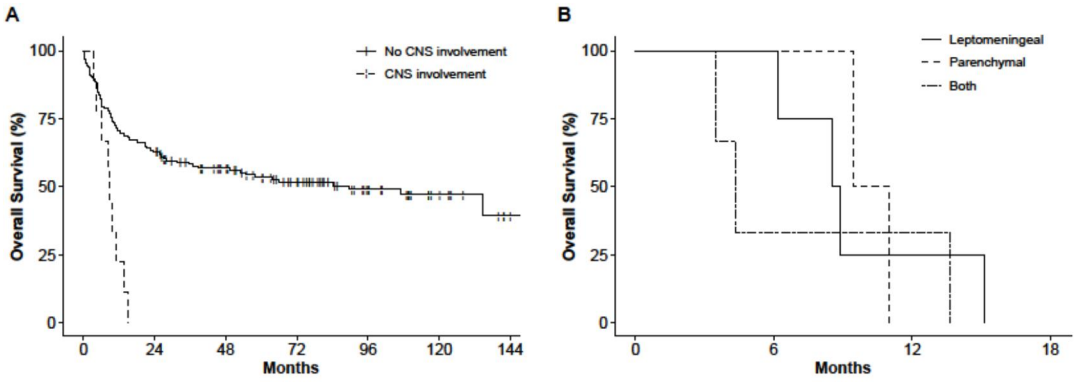

Fig 2. Overall survival by the presence and by the characteristics of secondary CNS involvement

(A) By the presence of secondary CNS involvement. Without CNS involvement = 89.7 months (95% CI, 32.0-147.4), with CNS involvement = 8.9 months (95% CI, 7.8-10.1), P < 0.001,

(B) By the characteristics of secondary CNS involvement. Leptomeningeal metastasis = 8.5 months (95% CI, 5.8-11.2), parenchymal = 9.4 months (95% CI, not estimated), both = 4.3 months (95% CI, 3.0-5.7), P = 0.796

9 patients (5.3%) developed secondary CNS involvement during follow-up. All cases occurred within 1 year from the initial diagnosis. The median time from diagnosis to secondary CNS involvement was 5.0 months (95% CI, 4.6-5.3 months). The cumulative incidence of secondary CNS involvement at 6 months was 4.9%. All 9 patients with secondary CNS involvement died. The median OS of patients with secondary CNS involvement was 8.9 months (95% CI, 7.8-10.1). The median OS after secondary CNS involvement was 3.4 months (95% CI, 1.3-5.4). The median OS for CNS-relapsed or progressed patients who had leptomeningeal disease (N=4), parenchymal disease (N=2), and who had both (N=3) were 8.5 months (95% CI, 5.8-11.2), 9.4 months (95% CI, not estimated), and 4.3 months (95% CI, 3.0-5.7), respectively. Three patients had CNS involvement as relapse while they had been in CR status. Among these 3, 2 had CNS relapse only. 6 had CNS involvement as disease progression.

4. Risk factor analysis for secondary CNS involvement

Table 2 shows univariate analysis results for potential risk factors for secondary CNS involvement. Advanced stage (III-IV) at diagnosis, PINK score of 2 and above, first-line treatment (non-anthracycline-based, anthracycline-based, and RT alone), and lung/pleural or peritoneal involvement at the initial diagnosis showed association with secondary CNS involvement. It should be noted that there are only 9 patients who were treated with radiotherapy with or without cisplatin in the entire patient population. Age > 60, high serum lactate dehydrogenase level, > 1 extranodal sites involvement, high international prognostic index (IPI), bone marrow, skin, gastrointestinal tract, kidney/adrenal gland involvement,

primary non-nasal lymphoma, distant lymph node involvement, the presence of detectable blood EBV DNA at diagnosis, and first-line treatment with high-dose methotrexate ($\geq$ 2g/m^2) containing regimen were not associated with increased risk of CNS relapse/progression.

Clinical characteristics of individual patients with CNS relapse/progression are shown in table 3.

Table 2. Univariate risk factor analysis for secondary CNS involvement

	Hazard ratio [95% CI]	P-value
Stage at diagnosis III/IV	5.8 [1.5-23.4]	0.013
PINK ≥ 2	5.4 [1.4-21.9]	0.017
CNS-IPI high	Not significant	
Non-nasal disease	Not significant	
Extranodal sites > 1	Not significant	
Initial lung/pleural involvement	12.5 [3.3-47.5]	<0.001
Initial peritoneal involvement	41.9 [7.4-236.9]	0.001
Initial bone marrow involvement	Not significant	
First-line treatment		
Non-anthracycline-based	Reference	0.017
Anthracycline-based	4.8 [1.1-21.3]	
RT ± cisplatin	13.5 [2.2-82.2]	
High-dose methotrexate (≥ 2g/m^2) containing first-line regimen	Not significant	

CNS, central nervous system; IPI, international prognostic index; PINK, prognostic index of natural killer lymphoma; RT, radiotherapy.

Table 3. Individual characteristics of patients with secondary CNS involvement

Sex	Age	Stage	IPI	PINK	Involved site at diagnosis	Response to first-line treatment	Relapse/ progression	No. of regimens given before	Time to CNS involvement (months)	Symptoms at CNS involvement	Pattern of CNS involvement	OS (months)	OS from CNS involvement (months)	Subsequent treatment after CNS involvement
F	63	IV	3	4	BM, Pleura, Spleen, Liver, Rectum, Peritoneum, LN	CR to CHOP	Relapse	1	5.2	Diplopia	Lepto-meninges	8.5	3.4	ESHAP, IT-triple
M	52	IV	1	2	Lung, LN	PD to CHOP	Progression	2	0.7	Arm, leg weakness, dysarthria	Brain parenchyma	11.0	10.3	WBRT, ESHAP
F	38	IV	1	2	Nasopharynx, LN,	PD to CHOP	Progression	1	1.9	Tingling sense, dysarthria, partial seizure	Both	4.3	2.4	SMILE, RT to brain mass
F	51	I	2	0	Nasopharynx	PD to RT with cisplatin	Progression	2	5.3	Facial palsy, leg weakness	Lepto-meninges	6.2	0.9	HD-MTX, IT-triple
M	65	IV	3	2	Nasopharynx, Skin, Subcutaneous tissue, LN	CR to SMILE	Relapse	1	10.0	Facial palsy, diplopia	Both	13.6	3.7	SMILE, IT-triple, B-NHL,
F	46	II	1	0	Nasal cavity, Orbit, Paranasal sinus	PD to CHOP -> SMILE	Progression	2	6.2	Facial palsy	Lepto-meninges	8.9	2.7	B-NHL, IT-triple
F	61	IV	5	4	Lung, Pleura, Pancreas, LN	CR to VIDL	Relapse	1	4.8	Facial palsy	Brain parenchyma	9.4	4.6	HD-MTX, Cytarabine, ICE-D, IT-triple
F	55	IV	2	3	Lung, Pleura, Bowel, Peritoneum, LN	PD to SMILE	Progression	1	2.3	Facial palsy	Both	3.5	1.2	HD-MTX, GDP
M	67	I	1	1	Nasopharynx	PD to RT with cisplatin	Progression	1	5.0	Leg weakness	Lepto-meninges	15.1	10.2	RT to lumbar meninges, IT-triple, VIDL

IPI, international prognostic index; CNS, central nervous system; OS, overall survival; BM, bone marrow; LN, lymph node; CR, complete remission; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; PD, progressive disease; WBRT, whole-brain radiotherapy; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide; intrathecal (IT)-triple, intrathecal triple chemotherapy (methotrexate, cytarabine, hydrocortisone); B-NHL, cycle A containing IT-triple, vincristine, methotrexate, ifosfamide, etoposide, cytarabine, dexamethasone followed by cycle B containing IT-triple, vincristine, methotrexate, cyclophosphamide, doxorubicin, dexamethasone; VIDL, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide; HD-MTX, high dose methotrexate; GDP, gemcitabine, dexamethasone, cisplatin; CCRT, concurrent chemoradiotherapy; RT, radiotherapy.

Discussion

In our study, 66.5% of patients received non-anthracycline-based chemotherapy. Secondary CNS relapse of ENKTL was uncommon (5.3%). This result is similar to that of previous studies which mostly included anthracycline-based-chemotherapy treated patients with the incidence of secondary CNS involvement between 3.7-5.8% [10,11]. It is also similar to the case of other aggressive lymphomas such as DLBCL (3-6% overall) [7,8,12] and PTCL (4-8% overall) [13-15], but much infrequent than that of highly aggressive lymphomas such as Burkitt lymphoma [16,17]. Secondary CNS involvement occurred early in the disease course with the median time from diagnosis to CNS involvement of 5.0 months. The survival outcomes of

these patients were dismal, with the median OS of 8.9 months. Patients with advanced stage, high PINK score, lung, peritoneal involvement, and patients who were treated with anthracycline-based chemotherapy or radiotherapy alone tended to experience more CNS involvement. Although there has been no clear evidence, the anatomical proximity between the nasal area and the CNS structures has given concern to the potential risk of the CNS involvement in ENKTL. Paranasal sinus involvement was once suggested as a risk factor for CNS relapse of PTCL and DLBCL in retrospective studies [13,18], although in DLBCL the idea was refuted by more recent studies [19]. However, despite its anatomical prevalence in the nasopharyngeal area the incidence of secondary CNS involvement was not higher than that of other aggressive lymphomas in our study.

Secondary CNS involvement of lymphoma, which included disease progression and relapse, occurred early in the disease course with the median time from diagnosis to the event of 5.0 months. This was consistent with previous reports in the anthracycline-based-chemotherapy era. Considering that most diagnostic studies for CNS disease were performed only after neurologic symptoms appeared, occult CNS disease might be already present at the time of the initial diagnosis even in cases of "secondary" CNS involvement. The prognosis of CNS-relapsed ENKTL was very poor with the median OS of 8.9 months, and all 9 patients had neurological symptoms. Considering that secondary CNS involvement is an early event and the patients experience debilitating neurological symptoms with markedly poor outcomes, early detection of CNS involvement is necessary. Including CNS-targeted diagnostic tools at the initial staging might help identify occult CNS lymphoma in asymptomatic, high-risk patients.

However, stratifying which patients are at higher risk of CNS relapse or progression is still an area of uncertainty. In our study, advanced disease status (Ann Arbor stage III/IV at the initial diagnosis), high PINK score (≥ 2), first-line treatment (non-anthracycline-based, anthracycline-based, and RT alone), and lung/pleural or peritoneal involvement at diagnosis were associated with higher incidence of secondary CNS involvement of ENKTL. Currently, only a handful of literature for secondary CNS involvement of T-cell origin lymphoma is available (Table 4). In these studies, advanced stage and multiple extranodal sites involvement showed association with secondary CNS involvement. Multiple extranodal sites involvement has been suggested as a risk factor for CNS relapse also in DLBCL [8]. In our study, > 1 extranodal sites involvement did not show statistically significant association with secondary CNS involvement, although the proportion of patients who had > 1 extranodal sites involvement was higher in the CNS-involved group. High NK/T cell lymphoma prognostic index (NKPI), which consists of the presence of B-symptom, advanced stage, high lactate dehydrogenase (LDH) level, and lymph node involvement, was once suggested as a potential risk factor for CNS relapse as it retained statistical significance after multivariate analysis in a previous study [10]. However, because our study population was mainly treated with non-anthracycline-based chemotherapy, we applied PINK score instead of NKPI [5,20]. As a result, PINK score of 2 and above showed association with increased secondary CNS involvement. It is uncertain whether there is an actual association between any specific organ involvement and secondary CNS involvement of ENKTL. In DLBCL, kidney and/or adrenal gland involvement showed association with CNS relapse thus implemented as a part of CNS-IPI [7]. However, no CNS-involved patient in our population had kidney nor adrenal gland involvement at diagnosis, and CNS-IPI was not associated

Table 4. Previous studies on the secondary CNS involvement of mature T- and NK-cell origin lymphomas [10,11,14,15]

Year, Author, Nation	Patient population	Rate of CNS inv. (ENKTL /entire group)	OS from CNS inv. (mo)	Time to CNS inv. (mo)	Univariate risk factor analysis	Multivariate risk factor analysis	CNS lesions
2010, Kim, Korea	ENKTL (N=208)	12/208 (5.8%)	2.5	6.0	LN inv. Extra upper aerodigestive primary Stage III-IV NKPI III-IV	NKPI III-IV	N-S
2015, Ellin, Sweden	T-cell lymphomas (N=625) ENKTL (N=26, 4.2%)	0/26 28/625 (4.5%)	1.1	4.3	Skin inv. GI inv. >1 EN site	Skin inv. GI inv. >1 EN site	LMS 64.3% Paren-chyme 35.7%
2016, Gurion, USA	T-cell lymphomas (N=231) ENKTL (N=17, 7.4%)	2/17 (11.8%) 15/231 (6.5%)	2.6	3.4	Stage III-IV BM inv. >1 EN site ATLL	>1 EN site IPI ≥ 3	N-S
2018, Chihara, USA	T-cell lymphomas (N=600) ENKTL (N=54, 9.0%)	2/54 (3.7%) 13/600 (2.2%)	1.5	6.4	>1 EN site	>1 EN site	LMS 100%
Current study	ENKTL (N=170)	9/170 (5.3%)	3.4	5.0	Stage III-IV PINK ≥ 2 Lung inv. Peritoneal inv.	Not done	LMS 44.4% Paren-chyme 22.2% Both 33.3%

CNS, central nervous system; ENKTL, extranodal NK/T-cell lymphoma, nasal type; OS, overall survival; inv., involvement; mo, months; LN, lymph node; NKPI, NK/T-cell lymphoma prognostic index; N-S, not specified; GI, gastrointestinal; EN, extranodal; LMS, leptomeningeal seeding; BM, bone marrow; ATLL, adult T-cell leukemia/lymphoma; IPI, international prognostic index; PINK, prognostic index of natural killer cell lymphoma.

with a higher CNS involvement rate. Skin and gastrointestinal tract involvement that were once suggested as risk factors for CNS involvement in PTCL [15] also did not show statistically significant association in our study. In our study, lung/pleural involvement and peritoneal involvement showed statistical significance in univariate Cox analysis, but this might be a mere representation of advanced disease status.

Lastly, first-line treatment (anthracycline-based or non-anthracycline-based) was associated with both overall survival and secondary CNS involvement in our study. It should be noted that although patients who were treated with radiotherapy with or without cisplatin showed high hazard ratio in our univariate risk factor analysis, there were only 9 patients who received such treatment in the entire patient population, therefore this result should be interpreted with caution. Previous anthracycline-based combination chemotherapy regimen was ineffective for the treatment of ENKTL [21-26]. But recently the outcome was significantly improved with the application of non-anthracycline-based treatment. In localized cases, combined radiotherapy and non-anthracycline chemotherapy regimens showed CR rate around 80% with 3-5Y overall survival over 70% [27-29]. Considering that secondary CNS involvement tends to occur more frequently in patients with advanced staged disease or higher prognostic score in our study, it is possible that better systemic disease control achieved with non-anthracycline-based chemotherapy led to lower incidence of the secondary involvement of ENKTL. Another possibility is that specific chemotherapeutic agents included in non-anthracycline-based chemotherapy but not anthracycline-based chemotherapy such as high-dose methotrexate had a protective effect against secondary CNS involvement of ENKTL, although first-line treatment with high-dose methotrexate containing regimen did not show statistically significant

association with secondary CNS involvement rate in this study. This study is not sufficient to evaluate the role of prophylactic intrathecal chemotherapy. Further studies with larger sample size are warranted regarding the protective effect of such treatment.

Aside from its retrospective nature, there are several limitations in our study. First, multivariate risk factor analysis was not feasible due to the small number of CNS-involved patients. Secondly, although CNS relapsed or progressed patients showed significantly poorer survival outcomes in our study, this could be mainly due to their concurrent systemic disease progression. It is true that non-anthracycline-based chemotherapy brought a major improvement in the outcome of ENKTL, but patients who were unresponsive to non-anthracycline-based chemotherapy still have a very poor outcome, regardless of the presence of CNS involvement [30]. Nonetheless, since all CNS-involved cases in our study had detrimental symptoms such as seizure or motor weakness from CNS lesions, appropriate control of CNS disease is important at the very least for improving patients' quality of life.

Conclusion

In conclusion, this study demonstrated that secondary CNS involvement of ENKTL in the non-anthracycline-based treatment era is still an uncommon, early event with a dismal outcome. For early detection, brain imaging or CSF analysis might be considered as a part of the initial diagnostic workup in high-risk patients.

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국문요약

서론: 비형 extranodal NK/T-세포 림프종 (ENKTL) 은 특이한 임상상을 보이는 비호지킨 림프종의 일종이다. 이 질환은 주로 코와 부비동 주변을 침범하는데, 이러한 구조물이 중추 신경계와 해부학적으로 가깝기는 하지만 실제 이 질환의 중추 신경계 이차 침범의 빈도나 임상상, 예후 등에 대해서는 잘 알려져 있지 않다. 이에 따라 그 치료 전략 역시 적은 수의 데이터에 근거하고 있는 실정이다.

연구 방법: 2003년 1월부터 2016년 6월까지 서울아산병원에서 ENKTL 로 진단받은 환자군이 연구에 포함되었으며, 진단 당시 중추 신경계 침범이 있었던 환자는 제외하였다. 중추 신경계 재발은 영상의학적 또는 병리학적으로 진단하였다. 카플란-마이어 곡선을 이용하여 생존 기간을 추정하였으며, 중추 신경계 재발의 위험인자를 확인하는 데에는 콕스 회귀분석을 이용하였다.

연구 결과: 총 170명의 환자가 연구에 포함되었다. 이들 중 109명 (64.1%) 이 남자였고, 진단 시 나이의 중앙값은 52세였다 (범위: 16-83). 진단 당시 병기가 I/II 였던 환자는 112명 (65.9%), III/IV 였던 환자는 58명 (34.1%) 이었다. 자연살해세포 림프종의 예후 점수 (prognostic index of natural killer cell lymphoma, PINK) 기준으로 저위험군, 중간 위험군, 고위험군은 각각 72명 (42.4%), 38명 (22.4%), 60명 (35.3%)이었다. 1차 치료로 33명 (19.3%)이 anthracycline 기반 항암치료를, 113명 (66.5%)이 비-anthracycline 기반 항암치료를 받았다. 중앙값 35.8개월간의 추적관찰 기간동안 9명 (5.3%)에서 중추신경계 침범이 발생하였다. 이 9명 중 4명은 연수막을 따라, 3명은 뇌 실질에, 2명은 2가지 모두로 전이하였다. 진단부터 중추신경계 재발까지 걸린 시간의 중앙값은 5.0 개월 (95% 신뢰구간: 1.3-5.4) 였다. 중추신경계 재발 유무에 따라 생존 기간에 유의미한 차이가 있었는데, 중추신경계 재발이 있었던 환자에서 전체 생존기간의 중앙값이 8.9 개월(95% 신뢰구간: 7.8-10.1) 이었던 것에 비해 중추신경계 재발이 없는 경우 89.7 개월 (95% CI, 32.0-147.4) 이었다 ($P < 0.001$). 단변량 콕스 회귀분석을 시행하였을 때, 진단시 병기가 III/IV기인 경우

(위험비 5.8 (95% 신뢰구간: 1.5−23.4), P = 0.013), 폐 또는 흉막 전이 (위험비 12.5 (95% 신뢰구간: 3.3−47.5), P < 0.001), 복막 전이가 있는 경우 (위험비 41.9 (95% 신뢰구간: 7.4−236.9), P = 0.001), PINK ≥ 2 (위험비 5.4 (95% 신뢰 구간: 1.4−21.9), P = 0.017), 1차 치료가 anthracycline 기반 항암치료였던 경우 (위험비 4.8 (95% 신뢰구간: 1.1−21.3), P = 0.017) 중추 신경계 재발과 통계적 연관성을 보였다. 중추 신경계 침범이 발생한 환자 수가 적어 다변량 분석은 시행하지 못하였다. 나이, 성별, 혈청 내 젖산탈수소효소 값, 임파선 외 전이 병소가 >1 개인 경우, 국제 예후 위험 인자 (international prognostic index, IPI) 또는 중추신경계 국제 예후 위험 인자 (CNS−IPI) 고위험군인 경우, 비−비형 ENKTL, 그리고 고농도 methotrexate (≥ 2g/m^2) 를 포함하는 일차 치료 여부는 모두 중추 신경계 재발과 통계적으로 유의한 연관성을 보이지 못하였다.

결론: 이번 연구에서는 ENKTL 의 중추 신경계 재발은 드물지만 그 예후는 매우 불량함을 보였다. 중추 신경계 재발은 대개 질병의 초기에 발생하므로, 일부 고위험군 환자에서는 진단 당시 중추 신경계 병변의 조기 확인 및 이에 따른 치료 방법의 결정이 필요할 수 있겠다.

중심 단어: 비형 extranodal NK/T−세포 림프종, 중추 신경계 재발