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Phase II Trial of Concurrent Radiation and Weekly Cisplatin Followed by VIPD Chemotherapy in Newly Diagnosed, Stage IE to IIE, Nasal, Extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma Study

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ABSTRACT

Purpose
On the basis of the benefits of frontline radiation in early-stage, extranodal, natural killer (NK)/T-cell lymphoma (ENKTL), we conducted a phase II trial of concurrent chemoradiotherapy (CCRT) followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD).

Patients and Methods
Thirty patients with newly diagnosed, stages IE to IIE, nasal ENKTL received CCRT (ie radiation 40 to 52.8 Gy and cisplatin 30 mg/m^2 weekly). Three cycles of VIPD (etoposide 100 mg/m^2 days 1 through 3, ifosfamide 1,200 mg/m^2 days 1 through 3, cisplatin 33 mg/m^2 days 1 through 3, and dexamethasone 40 mg days 1 through 4) were scheduled after CCRT.

Results
All patients completed CCRT, which resulted in 100% response that included 22 complete responses (CRs) and eight partial responses (PRs). The CR rate after CCRT was 73.3% (ie, 22 of 30 responses; 95% CI, 57.46 to 89.13). Twenty-six of 30 patients completed the planned three cycles of VIPD, whereas four patients did not because they withdrew (n = 2) or because they had an infection (n = 2). The overall response rate and the CR rate were 83.3% (ie; 25 of 30 responses; 95% CI, 65.28 to 94.36) and 80.0% (ie, 24 of 30 responses; 95% CI, 65.69 to 94.31), respectively. Only one patient experienced grade 3 toxicity during CCRT (nausea), whereas 12 of 29 patients experienced grade 4 neutropenia. The estimated 3-year, progression-free and overall survival rates were 85.19% (95% CI, 72.48 to 97.90) and 86.28% (95% CI, 73.97 to 98.59), respectively.

Conclusion
Patients with newly diagnosed, stages IE to IIE, nasal ENKTL are best treated with frontline CCRT.

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INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma (ENKTL) shows a poor response to anthracycline-based chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens,[1-3] because of the frequent expression of a multidrug-resistant P-glycoprotein.[4,5] The use of radiotherapy as initial treatment was reported to produce a greater complete response rate than chemotherapy.[6-8] However, when ENKTL is treated with radiation alone, local and systemic failures are observed frequently, even when the disease is in early stage, and especially within 2 years of the completion of treatment.[8-12] Therefore, a newer treatment strategy for stages IE to IIE ENKTL is required to improve response rate and survival. An association of radiation dose with response and survival was suggested previously,[12,13] but minimization of the radiation dose should be considered because of the adverse effects and the risk of secondary malignancy associated with the use of radiotherapy. Thus, we designed a concurrent chemoradiotherapy (CCRT) regimen with 40 Gy of radiation and weekly administration of cisplatin as a radiosensitizer. In addition, in consideration of the risk of systemic relapse after CCRT, we added systemic chemotherapy that consisted of ifosfamide and methotrexate, which are not affected by P-glycoprotein, and etoposide, which is known to be

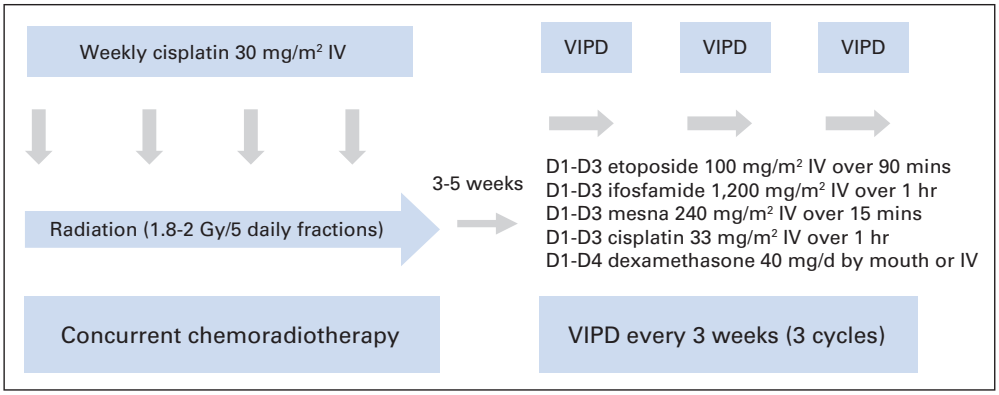

Fig 1. Treatment scheme. VIPD, etoposide, ifosfamide, cisplatin, and dexamethasone; IV, intravenous.

effective for Epstein-Barr virus (EBV) –associated lymphoproliferative disorders.[14,15] We report here the results of our phase II, prospective study that consisted of CCRT followed by systemic chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria

Thirty patients were enrolled from April 2006 to October 2007. To be eligible for enrollment, patients were required to have a biopsy-proven diagnosis of nasal ENKTL, to be at least 18 years old, to have disease classified as Ann Arbor stage IE or IIE, to have measurable disease, to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and to have a life expectancy greater than 12 weeks. Patients also had to have adequate hematologic function (ie, hemoglobin $\geq$ 9.0 g/dL, absolute neutrophil count $>$ 1,500/μL, and platelets $>$ 100,000/μL), renal function (ie, serum creatinine $\leq$ 1.5 mg/dL, creatinine clearance $\geq$ 50 mL/min), and hepatic function (ie, total bilirubin $\leq$ two times the upper limit of normal and AST $\leq$ three times upper limit of normal). Diagnosis of ENKTL was based on the presence of histologic features and immunophenotypes compatible with ENKTL (eg, cytoplasmic $CD3^+$, $CD20^-$, $CD56^+$, positive for cytotoxic molecules, positive for EBV by fluorescence in situ hybridization). The exclusion criteria were prior or concomitant malignant tumors and any coexisting medical problems of sufficient severity to prevent full compliance with the study protocol. ENKTL with non-nasal sites, such as skin or gastrointestinal tract, was excluded even if it was localized. Other subtypes of non-Hodgkin's lymphoma (NHL), including myeloid/NK cell precursor acute leukemia, blastic NK cell lymphoma/precursor NK cell lymphoblastic leukemia, aggressive NK cell leukemia, and peripheral T-cell lymphoma unspecified, were excluded. All patients provided written informed consent. This study was approved by the institute review board of each hospital.

Treatment and Dose Modifications

The treatment scheme is shown in Figure 1 and consisted of CCRT followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD). After immobilization of the patient, computed tomography (CT) simulation was performed to determine the appropriate radiation therapy doses for each patient. The radiation target volume covered the gross clinical lesions plus adequate margins. All patients received three-dimensional (3D) conformal radiation therapy by using 4 or 6 MV photons generated from a linear accelerator. The addition of elective lymphatic irradiation was determined on an individual basis. The median total dose to the gross lesion was 40 Gy, and the daily dose was 2 Gy for most patients, though it was 1.8 Gy for four patients. Three to five weeks after the completion of CCRT, VIPD chemotherapy was given every 3 weeks for up to three cycles (Fig 1). Because VIPD is a more-intensive regimen than CHOP or CHOP-like regimens, and because severe hematologic toxicities were observed in our pilot study, we chose three cycles of VIPD to avoid unnecessary toxicities. This treatment schema was derived from a pilot study of nine patients in whom we observed 100% objective response, including eight complete responses (CR) and one partial response (PR), after CCRT. The CRs were maintained after VIPD chemotherapy. However, all patients experienced febrile neutropenia, so we reduced the dosage of ifosfamide from 1,500 mg/m^2 to 1,200 mg/m^2 (Fig 1). All drugs were administered only if the absolute neutrophil count was greater than 1,500/μL and the platelet count was greater than 75,000/μL before each cycle. If either the neutrophils or platelets were lower than these levels, treatment was delayed for 7 days. Granulocyte colony-stimulating factor was administered for occurrences of grades 3 to 4 neutropenia. Dosages of ifosfamide and etoposide were reduced by 25% if absolute neutrophil counts and platelet counts recovered to 1,000 to 1,499/μL and to $\geq$ 50,000/μL, respectively, after a 1-week delay. If neutropenia (ie, absolute neutrophil count $<$ 1,000/μL) and thrombocytopenia (ie, platelets $<$ 50,000/μL) persisted for 2 weeks, the patient was withdrawn from this study. If patients experienced grade 2 or higher nonhematologic toxicities, treatment was interrupted until the toxicity resolved to grades 0 to 1. If creatinine clearance was less than 40 mL/min before a cycle, VIPD treatment was delayed for up to 2 weeks. VIPD was restarted after the creatinine clearance recovered to more than 40 mL/min. If the creatinine clearance did not recover, cisplatin was omitted from the next VIPD.

Evaluation

Baseline evaluation were performed 14 days or less before enrollment, and all patients were staged according to the Cotswold modification of the Ann Arbor staging system, which included history taking, physical examination, complete blood count, serum biochemistry with lactate dehydrogenase (LDH), bone marrow aspiration and trephine biopsy, endoscopic examination of the nasal and oral cavities by otorhinolaryngologists, CT scanning or magnetic resonance imaging (MRI) of the involved lesions, CT scanning of the chest and abdomen-pelvis, and positron emission tomography (PET). Quantitative polymerase chain reaction (PCR) for EBV DNA in peripheral blood also was performed to determine the EBV viral load. All of these studies were performed before treatment and after completion of CCRT and VIPD, and they were repeated every 3 to 6 months thereafter to monitor disease progression.

Assessment

Treatment response was assessed according to WHO criteria.[16] CR was defined as disappearance of all previously measurable lesions and absence of any new tumor lesions. PR was defined as a decrease of at least 50% in the product of two perpendicular diameters of each measurable lesion. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in tumor size, and progressive disease (PD) was defined as greater than 25% increase in the product of the two diameters of at least one tumor or as the presence of a newly developed lesion. Every patient received a laryngoscopic exam before and after CCRT and after completions of VIPD to confirm the pathologic CR. The primary end point was the response rate, which was calculated as the proportion of patients classified as CR and PR. The secondary end points were progression-free survival (PFS), overall survival (OS), and toxicity. PFS was defined as the time from the date of enrollment to the date of documented disease progression, and it was censored at the date of the last

follow-up visit. OS was measured from the date of enrollment to the date of death as a result of any cause, and it was censored at the date of the last follow-up visit. Toxicity was evaluated before each treatment cycle according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

Statistical Analysis

CR rates for stages IE to IIE ENKTL after radiotherapy were reported previously to be approximately 70%.[17,18] Therefore, we calculated sample size to be sufficient to reject a 70% CR rate in favor of a target CR rate of 90%, according to Simon's optimal two-stage design.[19] If a target level of interest is assumed as p1 = 0.90, and a lower activity level is assumed as p0 = 0.70, six patients needed to be accrued; if four or more CRs were observed, the trial would be continued. Planned accrual was for 27 patients; if CR was observed in 22 or more patients, the treatment would continue into a phase III trial. This design provided a probability of ≤ .05 of accepting a treatment worse than p0 and a probability of ≤ .20 for rejecting a treatment better than p1. If we assume that the dropout rate is 10%, the total accrual needed to be 30 patients. The Kaplan-Meier method was used to calculate PFS and OS, and survival curves were compared by the log-rank test. A two-sided *P* value of less than .05 was considered significant.

RESULTS

Characteristics of Patients

The characteristics of the patients are summarized in Table 1. The median age was 48.5 years (range, 23 to 73 years); 86.7% of all patients were younger than 60 years of age. All patients were in the low or low-intermediate risk categories of the International Prognostic Index. However, when we grouped patients on the basis of the NK/T cell lymphoma prognostic index (NKPI) proposed previously for ENKTL, which includes the presence of "B" symptoms, lesions at stages III or IV, elevated serum LDH concentration, and lymph node involvement,[20] nine patients belonged to group III or IV (ie, those with > two risk factors).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Patients No.	Patients %
Age, years		
≤ 60	26	86.7
> 60	4	13.3
Sex		
Male	17	56.7
Female	13	43.3
ECOG performance status		
0	17	56.7
1	13	43.3
Ann Arbor stage		
I	15	50.0
II	15	50.0
Serum LDH		
Normal	24	80.0
Increased	6	20.0
"B" symptoms		
Absent	19	63.3
Present	11	36.7
EBV titration, copies/μL		
< 64	19	63.3
≥ 64	11	36.7
LN involvement		
Absent	19	63.3
Present	11	36.7
Platelet count		
≤ 150,000/mm^3	3	10.0
> 150,000/mm^3	27	90.0
Absolute lymphocyte count		
≤ 1,000/mm^3	7	23.3
> 1,000/mm^3	23	76.7
IPI		
0/1	23	76.7
2	7	23.3
NK prognostic index group		
I/II	21	70.0
III/IV	9	30.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; EBV, Epstein-Barr virus; LN, lymph node; IPI, International Prognostic Index; NK, natural killer.

Response

In the first stage, six patients were entered onto the study, and five of these experienced CR. After this preliminary result, 30 patients were registered. After CCRT, the overall response rate, which included 22 CRs and eight PRs, was 100% (Fig 2). After VIPD chemotherapy, 19 patients retained CRs, and five patients with PRs to CCRT achieved CR (Fig 2). Twenty-four patients achieved CR after the completion of VIPD (CR rate, 80.0%; 95% CI, 65.69 to 94.31).

Relapse

Four (13.33%) of 30 patients experienced disease progression (95% CI, 1.17 to 25.49). Systemic progression was observed in one patient (a 60-year-old woman) when new lesions were found in her breast. After progression, she refused additional treatment, and she died 3 months later. Local disease progression was found in two patients: one patient (a 54-year-old man) experienced a relapse in the left nasal cavity within his previous radiation field, and the other patient (a 65-year-old man), who was still in PR after the completion of treatment, experienced disease progression in the laryngopharyngeal area just outside the border of the radiation field. Local as well as systemic relapse was found in one patient (a 58-year-old man). He experienced relapse in the nasal cavity and had multiple skin lesions (Fig 2). All three of these male patients were treated with the solumedrol, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) regimen.[21] However, only one patient (a 54-year-old man) remained alive after treatment at the time of this article.

Toxicity

Hematologic toxicity was minimal during CCRT; grades 1 to 2 leukopenia were observed in seven patients (23.3%, Table 2). Nonhematologic toxicities were tolerable, and most toxicities were grade 1. Although one patient had grade 3 nausea, he could continue treatment without interruption, because his nausea was controlled by supportive care. The other grade 2, nonhematologic toxicities were managed so there was no delay or interruption of CCRT. However, one patient (a 47-year-old man) dropped out after CCRT and withdrew his consent for personal reasons.

Grades 3 to 4 hematologic toxicities were frequent during VIPD. Anemia and thrombocytopenia were less severe in patients than was leukopenia (Table 2). Eight patients experienced grade 4 leukopenia. There were two deaths associated with complications because of infection: one patient (a 73-year-old man) died as a result of gram-positive

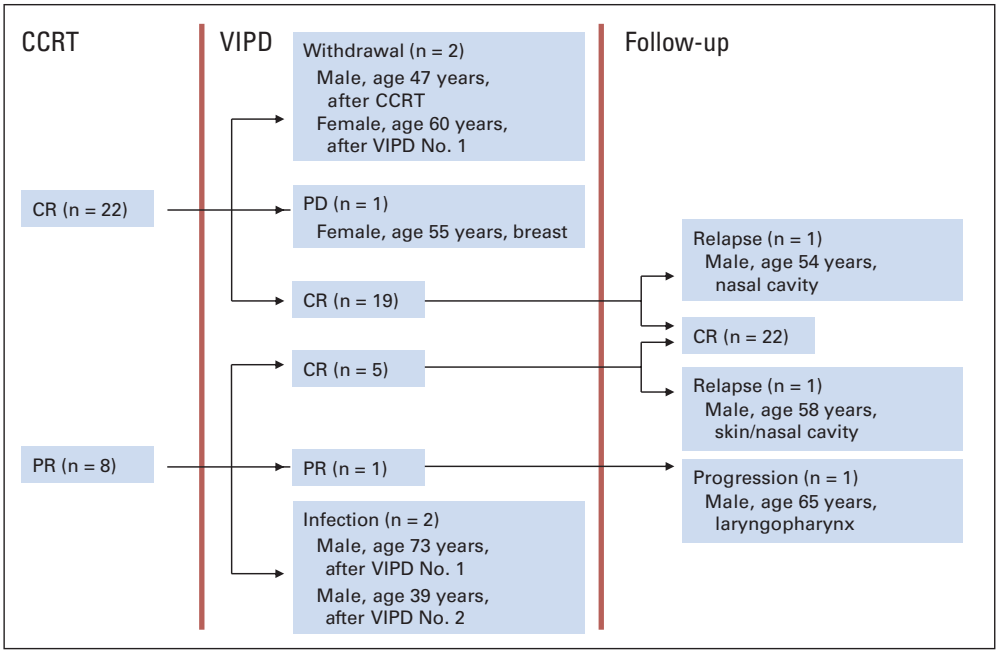

Fig 2. Summary of treatment outcomes and treatment failures. CCRT, concurrent chemoradiotherapy; CR, complete response; VIPD, etoposide, ifosfamide, cisplatin, and dexamethasone; PD, progressive disease; PR, partial response.

sepsis while neutropenic, and the other patient (a 39-year-old man) died before the start of the third cycle of VIPD. However, this death might be related to disease progression, because the patient was not neutropenic and because no microbiologic evidence of infection was found, although the final cause of his death was suspected to be septic shock. One patient (a 60-year-old woman) withdrew her consent after the first cycle of VIPD because of grade 3 hematologic toxicity (Fig 2).

Survival and Prognostic Factor Analysis

Three-year OS and PFS rates were 86.28% and 85.19%, respectively. These survival outcomes were superior to those for our previous patient cohort that was treated with dose-intensified CHOP followed by radiotherapy (Fig 3).[22] A platelet count less than 150,000/mm^3 and an absolute lymphocyte count less than 1,000/mm^3 were significant, poor prognostic factors for OS and PFS in univariate analysis ($P < .05$). When we dichotomized patients on the basis of the cutoff value of our previous report (ie, 64 copies/μL EBV DNA), elevated titer of EBV DNA ($\geq$ 64 copies/μL) was also associated with worse PFS ($P = .044$).[23] However, other parameters, including age, Ann Arbor stage, serum LDH, B symptoms, lymph node involvement, and International Prognostic Index, were not prognostic for OS and PFS. Multivariate analysis failed to show any independent prognostic factor for PFS and OS.

Table 2. Toxicity Profiles

	Adverse Event by Treatment Group and Event Grade							
	CCRT				VIPD			
Toxicity	1	2	3	4	1	2	3	4
Hematologic								
Anemia	10				4	11	7	1
Leukopenia	2	5			5	4	6	8
Thrombocytopenia						5	7	
Febrile neutropenia							15	3
Nonhematologic								
Nausea	13	10	1		10	7	1	
Vomiting	6	3			3	4	1	
Diarrhea	2				2			
Anorexia	5	1			5			
Constipation	2	1			4			
Stomatitis	7	4			5	1		
Azotemia						3		
Gastritis					1			
Neuropathy	6				6	1		

Abbreviations: CCRT, concurrent chemoradiotherapy; VIPD, etoposide, ifosfamide, cisplatin, and dexamethasone.

DISCUSSION

This study applied frontline treatment with CCRT followed by non–anthracycline-based chemotherapy for stages IE to IIE nasal ENKTL. For CCRT, we performed a weekly cisplatin administration as a radiosensitizer to augment the efficacy of radiotherapy as well as to reduce the amount of radiation. The CR rate after CCRT was 73.3%, which was superior to the rates reported in previous studies of chemotherapy followed by radiotherapy.[1-3] This CR rate was comparable to those reported in previous studies of treatment with radiotherapy alone,[12,18] but our radiation doses (median, 40 Gy; range, 40 to 52.8 Gy) were smaller than in previous studies, in which doses greater than 45 to 70 Gy were used. In this study, 19 patients received 40 Gy, nine patients received 40 to 44 Gy, one patient received 46 Gy, and one patient received 52.8 Gy. A previous study suggested that radiation doses of more than 52 Gy might be required to obtain in-field control in patients with localized ENKTL.[13] Another reported that a radiation dose of less than 45 Gy was significantly associated with local relapse.[12] However, we achieved satisfactory local control with acceptable toxicity by using CCRT.

VIPD chemotherapy was added to the regimen to prevent systemic relapse and for consolidation. Five patients who experienced

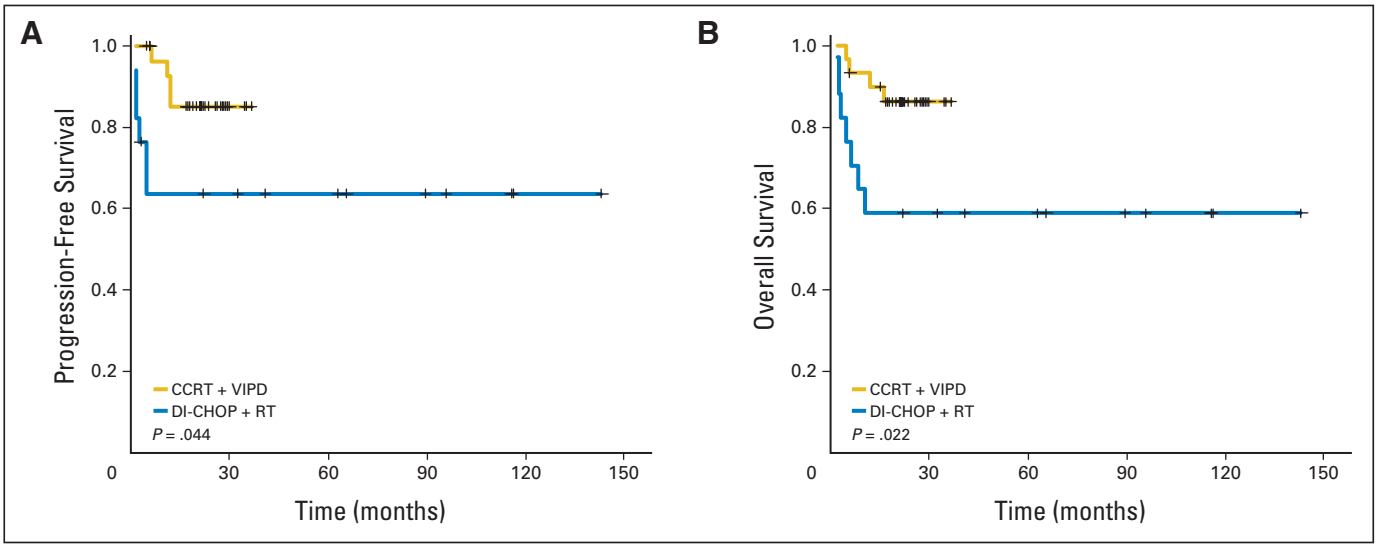

Fig 3. Concurrent chemoradiotherapy (CCRT) followed by etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) produced a significantly longer (A) progression-free survival and (B) overall survival than our previous patient cohort that was treated with dose-intensified (DI) cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy followed by radiotherapy (RT).

PRs then experienced conversion to CR after VIPD chemotherapy, which resulted in an 80.0% CR rate (ie, 24 or 30 patients; 95% CI, 65.69 to 94.31). Furthermore, only four patients experienced disease progression or relapse during follow-up: one was, systemic, two were local, and one was combined systemic and local relapse. Because the one local relapse occurred outside the radiation field, and because the other patient had simultaneous systemic relapse, the true local relapse rate was only 3.3% (ie, one of 30 patients), and the rate of systemic relapse was 10% (ie, three of 30 patients). A previous retrospective analysis of 102 patients treated with radiotherapy alone reported a higher local relapse rate (47%) and systemic relapse rate (27%).[12] In a recent nationwide analysis that included 105 patients with stages IE to IIE ENKTL, the local failure rate (29%) also was higher than the one we observed in our patients.[8] Therefore, our treatment strategy may reduce local relapse although it uses reduced doses of radiation. Although we observed three occurrences of systemic relapse, this rate was lower than that found in previous reports. In a comparison of these results with those of our previous cohort

Table 3. Study Comparison With Previous Major Series of Stage IE/IIE, Extranodal, NK/T-Cell Lymphomas

Study by Type	No. of Patients	Study Period	Treatment		RT Dose (Gy)		CR Rate (%)	Survival				Failure Rate (%)	
								OS		PFS			
			Type	No. of Patients	Median	Range		Type	Rate (%)	Type	Rate (%)	Local*	System†
Retrospective													
Koom et al[12]	102	1976-1998	RT alone		45	20-70	72	5 year	42	5 year	53	47	27
Li et al[8]	105	1983-2003	RT alone	31	50	40-65	83	5 year	66	5 year	61	29	81
			CT + RT‡				81	5 year	76	5 year	61		
			CT alone	3									
Cheung et al[6]	79	1977-2001	RT alone	18	50	30-60	77.8	5 year	29.8	5 year	30.5	46.7	75.6
			CT + RT‡	61			65.6	5 year	40.3	5 year	35.8		
Wang et al[24]	53	1997-2001	CT + RT§		45	36-50	81.1	2 year	75.8	2 year	61.8	18.9	15.1
Prospective													
Kim et al[1]	17	1995-1999	CT + RT‖		45		40	3 year	59	Not described		64.7	5.9
Lee et al[22]	17	2000-2004	CT + RT¶		44		76	3 year	67	3 year	56	11.8	29.4
This study	30	2006-2007	CCRT + CT		40	40-52.8	80	3 year	86.3	3 year	85.2	6.7	6.7

Abbreviations: NK, natural killer; RT, radiotherapy; CR, complete response; OS, overall survival; PFS, progression-free survival; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; CHOP, cyclophosphamide, adriamycin, vincristine, and prednisone.
*Local failure included locoregional relapse after treatment or progression during treatment.
†Systemic failure included systemic relapse after treatment or progression during treatment.
‡CHOP or CHOP-like treatment mainly were used.
§Six cycles of CHOP were administered and were followed by radiotherapy.
‖Four cycles of CHOP, followed by radiotherapy, were administered.
¶Two cycles of dose-intensified CHOP, followed by radiotherapy, were administered; after that, four cycles of CHOP were administered.

treated with dose-intensified CHOP followed by radiotherapy,[22] our systemic relapse rate (10%; ie, three of 30 patients) was lower (29.4%; ie, five of 17 patients). We conclude that VIPD chemotherapy as an adjuvant to CCRT was effective for reducing relapse and for augmenting the response achieved by CCRT.

There were frequent grades 3 to 4, hematologic toxicities during VIPD chemotherapy, even though we reduced the doses of ifosfamide because of the results of our pilot study. Although two patients died during VIPD, one death was not clearly associated with treatment toxicity, because the patient did not have neutropenia. We believe this death may have been related to disease progression and to ENKTL-associated hemophagocytosis with multiorgan failure, although we do not have enough evidence to be sure.

In this study, the 3-year OS and PFS rates were approximately 86.28% and 85.19%, respectively. Although the survival benefit should be demonstrated in a randomized, phase III study, it is not feasible to conduct a randomized study, because ENKTL is a rare disease. Thus, we compared the treatment outcome of our new treatment strategy with our previous cohort that was treated with dose-intensified CHOP followed by radiotherapy, because no published data with CCRT or intensive regimens are available to compare, and because dose-intensified CHOP is a more aggressive treatment strategy than conventional treatment.[22] As a result, the survival outcome of CCRT followed by VIPD was better than our previous cohort (Fig 3). This treatment outcome is better than previous studies of radiotherapy alone or of combined modalities, including chemotherapy and radiotherapy (Table 3). A recent, international, peripheral T-cell leukemia study showed that the 3-year OS of stages I to II ENKTL was less than 50%.[25] Although our follow-up time was relatively short, most relapses were reported to occur early after treatment.[25] Thus, the survival outcomes that we observed attest to the effectiveness of CCRT followed by VIPD chemotherapy. At present, we still did not find any kinds of long-term toxicity among survivors, although our follow-up time was relatively short. But our cohort should be observed additionally to monitor the development of long-term toxicity, including secondary malignancy. In conclusion, CCRT followed by VIPD chemotherapy can be a feasible and effective treatment strategy for stages IE to IIE nasal ENKTL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Collection and assembly of data: Seok Jin Kim
Data analysis and interpretation: Seok Jin Kim
Manuscript writing: Seok Jin Kim
Final approval of manuscript: Won Seog Kim

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