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Original Articles

Treatment outcome of nasal NK-cell lymphoma : A report of 12 consecutively-diagnosed cases and a review of the literature

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We retrospectively reviewed the clinical courses of 12 consecutively-diagnosed cases of localized, nasal NK-cell lymphoma. All patients revealed a phenotype of CD2+CD3(Leu4)-cytoplasmic CD3ε+ CD5−CD45+CD56+. Nine patients were stage I, and three stage II. Seven patients were initially treated with an anthracycline-containing regimen (Group 1). All but one patient failed to achieve a complete response (CR) and died of lymphoma within six months of diagnosis. All patients with B symptoms and/or an elevated serum LDH level in Group 1 died. The remaining five patients were treated first with radiotherapy (Group 2). After radiotherapy, two patients were treated with anthracycline-containing regimens, and one patient was treated with carboplatin, etoposide, ifosfamide, and dexamethasone (DeVIC). Two patients were treated concurrently with radiotherapy and DeVIC (RT-DeVIC) : one showed B symptoms, and both had high serum LDH levels. All five patients in Group 2 achieved CR and four patients are alive with no evidence of recurrence. Based on the present study and a review of the literature, radiotherapy followed by, or combined with, chemotherapy is highly recommended as the initial treatment modality for localized nasal NK-cell lymphoma.
Key words radiotherapy, chemotherapy, drug resistance

INTRODUCTION

Extranodal, natural killer (NK)/T-cell lymphoma[1], formerly known as angiocentric lymphoma[2,3], is much more common in Asia and Latin America than in the United States and Europe[1−4]. In Japan, nasal NK/T-cell lymphoma accounts for 1.85% of all malignant lymphomas and NK/T-cell lymphoma of extranodal sites, other than the nose, accounts for 0.75%[5]. Extranodal NK/T-cell lymphoma is an Epstein-Barr virus (EBV)-associated neoplasm that is believed to consist of NK cells in most cases and possibly of T cells in others[2,3]. NK/T-cell lymphoma of extranodal sites other than the nose is reported to be incurable and is almost always fatal[6,7], while nasal NK/T-cell lymphoma has a more favorable outcome. Reported 5-year overall survival rates of nasal NK/T-cell lymphoma have ranged from 14 to 87%[6,8−24]. Approximately 90% of patients with nasal NK/T-cell lymphoma present with localized disease[6], and the prognosis of patients with relapsed disease is extremely poor[20]. Therefore, a more effective therapeutic regimen for localized nasal NK/T-cell lymphoma is needed.

In many studies, lymphomas arising in the nasal cavity and paranasal sinuses were not evaluated separately because it has been believed that any differences between them were not apparent[25]. Moreover, 'true' NK-cell lymphoma, peripheral T-cell lymphoma, and B-cell lymphoma were often included in one study because of the difficulty in immunophenotyping.

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Therefore, the specific therapeutic outcome of nasal NK-cell lymphoma has not been thoroughly examined.

Nasal NK/T-cell lymphoma is known to be resistant to conventional chemotherapy, and according to the literature most patients have been treated with radiotherapy (RT) with or without chemotherapy[6,8–24]. However, the details of treatment, especially the timing of RT and chemotherapy, are uncertain in many reports.

To clarify treatment details we retrospectively reviewed the clinical courses of consecutively-diagnosed cases of localized nasal NK-cell lymphoma.

Patients, Materials and Methods

Patients

Between 1988 and 2000, we diagnosed 12 patients with nasal NK-cell lymphoma. Eight patients (Cases 1–8) were included in our previous report concerning immunophenotypes[26]. Nasal tissue and/or lymph node specimens were obtained from patients after informed consent. Immunohistochemical staining with frozen sections was performed in all cases.

Histology and Immunohistochemistry

Histological diagnosis was carried out on hematoxilin-eosin stained, 10% formalin-fixed sections according to the WHO classification[1]. The immunophenotypic study of tumor cells was performed using a labeled avidin-biotin method on the frozen sections, as described previously [27]. New fuchsin and naphthol AS-BI phosphate were used as substrate-chromogen reagents. Sections were counterstained with Gill's hematoxylin. The monoclonal antibodies used were Leu5b (CD2), Leu4 (CD3), and Leu1 (CD5), (Becton Dickinson, Mountain View, CA); NKH1 (CD56) (Coulter, Hialeah, FL); CD3, L26 (CD20), and LCA (CD45), (DAKO, Carpinteria, CA).

Management

Seven patients were initially treated by combination chemotherapy (Group 1), and the remaining five patients were started on RT as soon as possible after diagnosis (Group 2). Three of them received consolidation chemotherapy after RT. Since 1998, patients have been treated concurrently with RT and chemotherapy.

All treatment protocols in RT used a conventional fraction schedule of 1.5–2.0 Gy/day, five times per week. The planned total dose to the involved area was 40–50 Gy. For patients with stage II disease the fields were extended to encompass the involved paranasal sinuses or cervical lymph nodes. Three patients received prophylactic cervical lymph node irradiation.

Nine patients received chemotherapy with anthracycline-containing regimens, and three were treated with a combination of carboplatin (CBDCA), etoposide (VP16), ifosfamide (IFM), and dexamethasone (DMX) [DeVIC] [28].

Clinical response was evaluated after induction therapy. A complete response (CR) was defined as the disappearance of all clinical evidence of disease and normalization of all laboratory values and image studies.

Statistics

Duration of survival was calculated from the time of diagnosis to the date of last follow-up or death. Overall survival was analyzed by the Kaplan-Meier method and was compared by means of the log-rank test.

Results

Patient characteristics of the 12 nasal NK-cell lymphoma cases

Twelve patients were diagnosed with nasal NK-cell lymphoma. All patients revealed a phenotype of CD2+CD3(Leu4)-cytoplasmic CD3ε+CD5−CD45+CD56+. The clinical features at presentation of these 12 patients with nasal NK-cell lymphoma are summarized in Table 1. Eight were male and four were female. The median age was 64/65 years, with a range of 41 to 78. Five patients (Cases 1, 4, 10, and 12) had only intranasal disease at presentation. In six patients, tumors extended beyond the nasal cavity and into neighboring sites, such as the paranasal sinuses, palate, and epipharynx. Three patients had involvement of cervical lymph nodes. Nine patients were stage I, and three stage II. Five patients presented with B symptoms. Serum LDH level was elevated in three patients, and performance status was higher than

Table 1. Characteristics of 12 patients with nasal NK-cell lymphoma

	Age/Sex	Sites of involvement	Stage	sLDH > N	PS > 1	IPI
1	56/F	nasal cavity	IA	No	No	L
2	44/M	nasal cavity, cervical lymph nodes	IIA	No	No	L
3	78/M	nasal cavity, paranasal sinuses, palate, orbit	IB	Yes	Yes	H
4	73/M	nasal cavity	IA	No	No	L
5	41/F	nasal cavity, cervical lymph nodes	IIA	No	No	L
6	67/M	nasal cavity, paranasal sinuses, orbit	IA	No	No	LI
7	66/M	nasal cavity, paranasal sinuses	IA	No	No	L
8	65/M	nasal cavity, paranasal sinuses	IB	No	Yes	LI
9	64/F	nasal cavity, palate, tonsil, cervical lymph nodes	IIB	No	No	LI
10	53/M	nasal cavity	IB	No	No	L
11	60/M	nasal cavity, palate, epipharynx	IB	Yes	No	LI
12	78/F	nasal cavity	IA	Yes	No	LI

H, high ; IPI, International Prognostic Index ; L, low ; LI, low intermediate ; N, normal ; PS, performance status ; sLDH, serum lactate dehydrogenase.

Table 2. Therapeutic outcome of patients initially treated with chemotherapy (Group 1)

	Age/Sex	Chemotherapy	RT	Response	Outcome, mo
2	44/M	VEPA-B x1, M-FEPA x2	None	NC	DOD, 3
3	78/M	CHOP x3	None	NC	DOD, 2
5	41/F	FARM	None	CR	AND, 104
6	67/M	VEPA-B x1	nasal cavity～ paranasal sinuses, 30 Gy	NC	DOD, 2
8	65/M	CHOP x1	nasal cavity～ mesopharynx, 4 Gy	NC	DOD, 1
9	64/F	VEPA-B x1	nasal cavity and cervical lymph nodes, 40 Gy	NC	DOD, 2
10	53/M	CHOP x1, DeVIC x1	nasal cavity and cervical lymph nodes, 50 Gy	NC	DOD, 6

AND, alive with no evidence of disease ; CR, complete response ; DOD, dead of disease ; NC, no change ; RT, radiotherapy.

one in two patients. According to the International Prognostic Index[29], six patients were classified as having low, five low intermediate, and one high.

Therapeutic outcome of patients initially treated with chemotherapies only (Group 1)

Table 2 shows the therapeutic regimens and outcomes of seven patients initially treated with chemotherapies only. All patients were treated with anthracycline-containing regimens : vincristine, cyclophosphamide, prednisolone, doxorubicin, and bleomycin (VEPA-B) in Cases 2, 6, and 9 ; cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in Cases 3, 8, and 10 ; methotrexate, vindesine, cyclophosphamide, prednisolone, and doxorubicin (M-FEPA) in case 2 ; epirubicin, cyclophosphamide, vincristine, VP16, methotrexate, prednisolone, mitoxantrone, IFM, vindesine, dacarbazine, and bleomycin (FARM) in case 5 ; and DeVIC in Case 10.

All but one patient (Case 5) failed to achieve CR. Four received additional RT, but died of lymphoma within six months of diagnosis. All patients with B symptoms and/or elevated serum LDH level died. One patient (Case 5) achieved CR and is alive with no evidence of disease.

Therapeutic outcome of patients initially treated with RT (Group 2)

Table 3 shows the therapeutic outcomes of patients initially treated with RT. Three patients were treated with RT and consolidation chemotherapy. Anthracycline-containing regimens were used in two patients : VEPA-B and M-FEPA in case 1, cyclophosphamide, epirubicin, vincristine, VP16, and prednisolone (CEOP plus VP16) in Case 2. One patient (Case 7) was treated with DeVIC after RT. Two patients diagnosed after 1998 were treated with RT and DeVIC concurrently. All five achieved CR. One patient (Case 1) died of relapsed lymphoma 19 months after diagnosis, the others are alive with no evidence of recurrence.

One patient (Case 11) who showed B symptoms (elevated fever, night sweats, and weight loss : 8 kg/3 mo) and elevated serum LDH level received RT-DeVIC therapy. He was treated

Table 3. Therapeutic outcome of patients initially treated with RT (Group 2)

	Age/Sex	RT	Chemotherapy	Response	Outcome, mo
1	56/F	nasal cavity, 50 Gy ; cervical lymph nodes, 30 Gy	VEPA-B x1, M-FEPA x1	CR, local relapse	DOD, 19
4	73/M	nasal cavity, 42 Gy ; cervical lymph nodes, 30 Gy	CEOP plus VP16 x3	CR	AND, 96
7	66/M	nasal cavity, 44 Gy ; cervical lymph nodes, 30Gy	DeVIC x6	CR	AND, 96
11*	60/M	nasal cavity～epipharynx, 45 Gy	DeVIC x6	CR	AND, 32
12*	78/F	nasal cavity, 40 Gy	DeVIC (75% dose) x3	CR	AND, 12

*treated concurrently with RT and DeVIC (RT-DeVIC).

AND, alive with no evidence of disease ; CR, complete response ; DOD, dead of disease ; RT, radiotherapy.

with 45 Gy of local RT, and simultaneously initiated with six courses of DeVIC therapy (CBDCA 300 mg/m² iv Day 1, VP16 100 mg/m² iv Day 1-3, IFM 1.5 g/m² iv Day 1-3, and DMX 40 mg/body iv Day 1-3 ; every 21 days). His nasopalatal and pharyngeal masses disappeared within one month after initial therapy, and clinical symptoms and abnormal findings on laboratory data improved rapidly and returned to normal after three courses of chemotherapy. Mucositis (Grade 3) developed during the third and fourth courses of DeVIC. There is no evidence of recurrence 32 months after diagnosis.

Another patient treated with RT-DeVIC therapy (Case 12) was an elderly female. She was treated with 40 Gy of local RT, and simultaneously initiated with three courses of DeVIC therapy (75% dose). Her nasal mass disappeared within one month after initiating therapy. Sinusitis (Grade 2) developed temporarily, but was resolved completely by medication. There is no evidence of recurrence 12 months after her diagnosis.

Survival

The 5-year overall survival rate was 39% (Fig. 1). Patients who received RT first (Group 2) showed a survival curve significantly superior to that for patients who received chemotherapy (Group 1) (P=.017, Fig. 2).

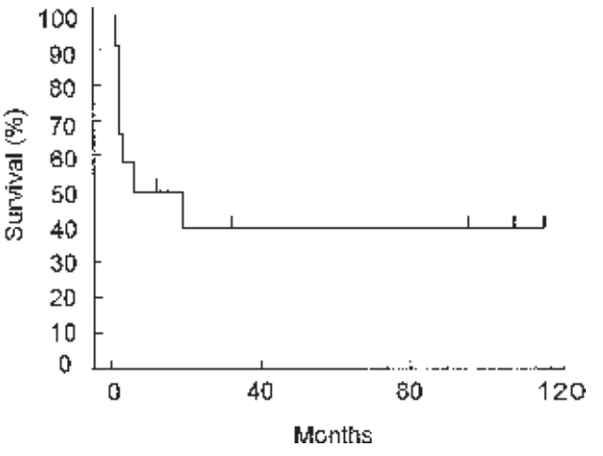

Fig. 1. Overall survival of 12 nasal NK-cell lymphoma cases.

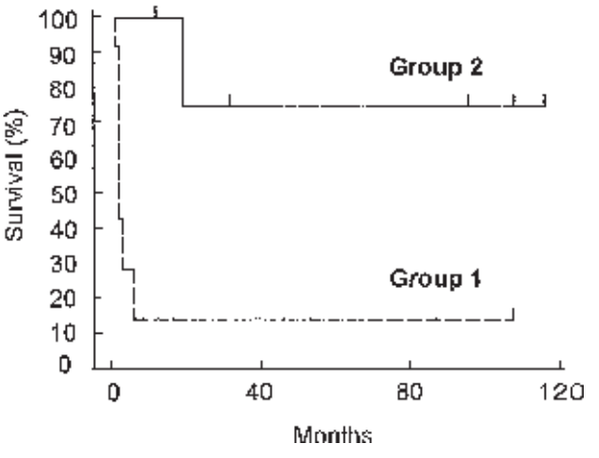

Fig. 2. Overall survival for patients in Group 1 and Group 2.

DISCUSSION

We reviewed the treatment outcomes of 12 nasal NK-cell lymphomas, and found that patients treated with chemotherapy alone had poorer outcomes than those initially treated by RT. Only one patient who presented B symptoms

Table 4. Outcome of nasal lymphoma according to treatment

Treatment	Diagnosis	Stage	N	5 yr OS	Reference
Cx → RT	NK/T or B-cell lymphoma	I, II	28	53–58%	Liang et al[8]
Cx → RT	NK/T-cell lymphoma	I, II	7	14%	Yu et al[10]
Cx (→ RT)	CD56+ NK lymphoma	I	18	28%	Kwong et al[11]
RT	NK/T or B-cell lymphoma	I, II	39	41%	Liang et al[8]
RT	angiocentric lymphoma	I, II	92	40%	Kim et al[20]
RT (→ Cx)	NK/T-cell lymphoma	I, II	11	45%	Nakamura et al[12]
RT (→ Cx)	NK/T or B-cell lymphoma	I	25	80%	Shikama et al[14]
RT (→ Cx)	NK/T or B-cell lymphoma	I	133	75%	Li et al[18]
RT → Cx	NK/T-cell lymphoma	I, II	57	87%(8yr)	Aviles et al[21]

Cx, chemotherapy ; OS, overall survival ; RT, radiotherapy.

obtained CR. Two patients who were treated by RT-DeVIC therapy achieved CR, and none involved severe adverse events.

Due to the low incidence of this disease, there has been no prospective study for localized, nasal NK-cell lymphoma. After reviewing the literature, we selected reports containing well-documented details of therapies, and have listed the results in Table 4. In the series by Yu, et al. [10], seven patients had combination chemotherapy followed by RT. The 5-year overall survival rate was 14%, a result similar ours. In 18 cases of CD56-positive localized (stage I) nasal NK lymphoma, reported by Kwong, et al. [11], the 5-year overall survival rate was 28%. Liang, et al. [8], reported a more favorable result, but their study included both NK/T-cell lymphoma and B-cell lymphoma. In patients who received only RT, the 5-year overall survival rates were approximately 40% [8,20]. Therefore, RT alone is not sufficient to obtain a cure. Patients who were treated with RT followed by chemotherapy seemed to exhibit a good prognosis[12,14,18,21], similar in outcome to ours. Based on the present study and a review of the literature, RT is highly recommended as the first therapy for localized nasal NK-cell lymphoma.

We have used RT-DeVIC therapy as our first-line therapy for localized nasal NK-cell lymphoma since 1998. RT-DeVIC is a concurrent regimen consisting of involved-field RT and DeVIC. DeVIC was designed as a salvage chemotherapeutic regimen for aggressive non-Hodgkin's lymphoma[28].

Previously, we examined the expression of P-glycoprotein, which is the product of the multi-drug resistance (MDR) 1 gene[30,31] in nasal NK/T-cell lymphoma cells, to clarify the mechanisms of drug resistance[32]. We found frequent expression of P-glycoprotein on nasal NK/T-cell lymphoma cells. Therefore, we can recommend not using MDR-related drugs or using P-glycoprotein/MDR1 modulators for nasal NK/T-cell lymphoma. The reason we selected DeVIC as a chemotherapeutic regimen for nasal NK-cell lymphoma is that DeVIC consists of CBDCA and IFM, which are MDR-unrelated anticancer agents[33,34]. Indeed, DeVIC showed temporary efficacy in a patient with refractory NK/T-cell lymphoma.

As in our Cases 8 and 9, highly aggressive cases of localized nasal NK-cell lymphoma do exist. In fact, the reported survival curve of nasal lymphoma declines within a few months after diagnosis[6,8,13,16]. Since we speculated that RT and chemotherapy separately are insufficient for such highly aggressive cases, we designed RT-DeVIC therapy to be a concurrent treatment with RT and chemotherapy. Concurrent therapies are commonly used in non-hematologic malignancies, for example in esophageal cancer[35] and lung cancer[36]. Since CBDCA enhances the efficacy of RT[37], it is widely used with RT. Our two patients treated with RT-DeVIC therapy did not show any severe adverse effects. Although they showed a high serum LDH level and/or B symptoms, they achieved CR.

From the results of this study and a review of the literature, RT is highly recommended as an initial therapy for localized nasal NK-cell lymphoma. The efficacy of RT-DeVIC therapy should be evaluated by a prospective, multi-institutional study.

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