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 lymphoma1), formerly known as angiocentric lymphoma2), is much more common in Asia and Latin America than in the United States and Europe3). 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 others6). NK/T-cell lymphoma of extranodal sites other than the nose is reported to be incurable and is almost always fatal6,7), 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 disease6, and the prognosis of patients with relapsed disease is extremely poor25). 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 apparent26). 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.\(^6,7\) 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.\(^6,7\) Nasal
tissue and/or lymph node specimens were
obtained from patients after informed consent.
Immunohistochemical staining with frozen sec-
tions 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 Dick-
inson, Mountain View, CA); NKH1 (CD56)
(Coulter, Hialeah, FL); CD3, L26 (CD20), and
LCA (CD45), (DAKO, Carpinteria, CA).

**Management**

Seven patients were initially treated by com-
ination chemotherapy (Group 1), and the remain-
ing 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 concurrent-
ly with RT and chemotherapy.
All treatment protocols in RT used a conven-
tional 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 induc-
tion therapy. A complete response (CR) was
defined as the disappearance of all clinical evi-
dence of disease and normalization of all labora-
atory 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 fea-
tures 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 cav-
ity and into neighboring sites, such as the par-
anasal 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 symp-
toms. Serum LDH level was elevated in three
patients, and performance status was higher than
nasal NK-cell lymphoma

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

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Sites of involvement</th>
<th>Stage</th>
<th>sLDH &gt; N</th>
<th>PS &gt; 1</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 56/F</td>
<td>nasal cavity</td>
<td>IA</td>
<td>No</td>
<td>No</td>
<td>L</td>
</tr>
<tr>
<td>2 44/M</td>
<td>nasal cavity, cervical lymph nodes</td>
<td>IA</td>
<td>No</td>
<td>No</td>
<td>L</td>
</tr>
<tr>
<td>3 78/M</td>
<td>nasal cavity, pananasal sinuses, palate, orbit</td>
<td>IB</td>
<td>Yes</td>
<td>Yes</td>
<td>H</td>
</tr>
<tr>
<td>4 73/M</td>
<td>nasal cavity</td>
<td>IA</td>
<td>No</td>
<td>No</td>
<td>L</td>
</tr>
<tr>
<td>5 41/F</td>
<td>nasal cavity, cervical lymph nodes</td>
<td>IA</td>
<td>No</td>
<td>No</td>
<td>L</td>
</tr>
<tr>
<td>6 67/M</td>
<td>nasal cavity, pananasal sinuses, orbit</td>
<td>IA</td>
<td>No</td>
<td>No</td>
<td>L</td>
</tr>
<tr>
<td>7 66/M</td>
<td>nasal cavity, pananasal sinuses</td>
<td>IA</td>
<td>No</td>
<td>No</td>
<td>L</td>
</tr>
<tr>
<td>8 65/M</td>
<td>nasal cavity, pananasal sinuses</td>
<td>IB</td>
<td>No</td>
<td>Yes</td>
<td>LI</td>
</tr>
<tr>
<td>9 64/F</td>
<td>nasal cavity, palate, tonsil, cervical lymph nodes</td>
<td>IB</td>
<td>No</td>
<td>No</td>
<td>LI</td>
</tr>
<tr>
<td>10 53/M</td>
<td>nasal cavity</td>
<td>IB</td>
<td>No</td>
<td>No</td>
<td>L</td>
</tr>
<tr>
<td>11 60/M</td>
<td>nasal cavity, palate, epipharynx</td>
<td>IB</td>
<td>Yes</td>
<td>No</td>
<td>LI</td>
</tr>
<tr>
<td>12 78/F</td>
<td>nasal cavity</td>
<td>IA</td>
<td>Yes</td>
<td>No</td>
<td>LI</td>
</tr>
</tbody>
</table>

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)

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

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

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...
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).

**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

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

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. 19, 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. 9, 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 prognosis12,14,16,21, 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 lymphoma28.

Previously, we examined the expression of P-glycoprotein, which is the product of the multi-drug resistance (MDR) 1 gene8,23 in nasal NK/T-cell lymphoma cells, to clarify the mechanisms of drug resistance32. 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 agents33,34. 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 diagnosis6,8,13,14. 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 cancer35 and lung cancer36. Since CBDCA enhances the efficacy of RT37, 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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