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Therapeutic Outcome of Extranodal NK/T-Cell Lymphoma Initially Treated with Chemotherapy

Result of Chemotherapy in NK/T-Cell Lymphoma

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The therapeutic outcome of chemotherapy in NK/T cell lymphoma (NTCL) has not been well documented until now. The aims of this study were to investigate the outcome of chemotherapy and to evaluate the clinical factors influencing the responsiveness to chemotherapy. Between 1995 and 2000, 59 patients received anthracycline-based chemotherapy as an initial treatment. Forty-five patients had nasal NTCL, whereas 14 had extranasal NTCL. Forty-one patients had stage I/II and 18 had stage III/IV disease. Epstein-Barr virus status was positive in 67.6% of cases. The results of initial chemotherapy were complete remission in 35.6% of the patients, 2-year disease-free survival in 22.9% and 2-year overall survival in 44.2%. Adjuvant radiotherapy after chemotherapy did not improve outcome in stage I/II nasal NTCL. The International Prognostic Index was a significant prognostic factor of complete remission rate, and stage was also significant for disease-free survival.

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NK/T cell lymphoma (NTCL) is a lymphoid malignancy that is thought to be of natural killer (NK) cell origin (1). This entity is rare in Western populations, but is more common among Orientals, Mexicans and South Americans of native American heritage. A recent nationwide study of malignant lymphomas in Korea revealed that NTCL accounted for 8.7% of all non-Hodgkin's lymphoma and for 74.1% of lymphomas arising in the nasal cavity and paranasal sinuses (2).

It was named 'angiocentric lymphoma' in the revised European–American lymphoma (REAL) classification based on its angiocentric histologic pattern (3). Jaffe et al. suggested that the term 'nasal NK/T cell lymphoma' was more appropriate than 'angiocentric lymphoma' (4). This terminology is also adopted in a new WHO classification (5). NTCL also develops outside the nose and frequently involves the skin, liver, soft tissue and the gastrointestinal (GI) tract (6). It is referred to as 'extranasal NTCL'.

Radiotherapy was initially effective in stage I/II nasal NTCL, but final outcome was unsatisfactory because of the frequent systemic progression or relapse (7–12). Many investigators have therefore suggested that radiotherapy should be combined with chemotherapy. In stage III/IV nasal and extranasal NTCL, combination chemotherapy is essential owing to their systemic nature. However, the role of chemotherapy as initial treatment has not been established because previous studies of chemotherapy included heterogeneous patient groups and their sample size was relatively small.

In the present study, we analyzed therapeutic outcome in patients with NTCL treated with an anthracycline-based combination chemotherapy as first-line treatment. We also sought to identify the prognostic factors affecting the responsiveness to chemotherapy.

MATERIAL AND METHODS

Patients

From January 1995 to July 2000, patients newly diagnosed with angiocentric lymphoma or NK/T cell lymphoma were included in the study. Their pathologic slides were reviewed by two pathologists and classified according to the REAL

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classification (1994) and the criteria suggested by Jaffe et al. (4). Nasal and upper aerodigestive cases that showed typical histologic features were included in this study irrespective of CD56 expression, but both CD56 expression and typical histologic findings were required in cases of extranasal disease. Immunophenotyping was performed on frozen sections or paraffin-embedded tissues for CD3, CD20, CD45RO and CD56. Epstein-Barr virus (EBV) was detected by *in situ* hybridization using an antisense riboprobe to EBER 1/2. Patients were staged according to the Ann Arbor system. Staging investigations included complete history and physical examination, a plain chest radiograph, complete blood counts, liver function tests, lactose dehydrogenase (LDH), marrow aspiration and trephine biopsy, and abdominal computed tomography (CT). CT or magnetic resonance imaging (MRI) was performed to give an accurate evaluation of the primary lesion.

Chemotherapy

CHOP (cyclophosphamide 750 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; vincristine 1.4 mg/m^2 i.v. day 1; prednisolone 60 mg/m^2 p.o. days 1–5) had been performed as the initial treatment until 1997 and then COPBLAM-V (cyclophosphamide 400 mg/m^2 i.v. day 1; vincristine 1 mg/m^2 i.v. infusion days 1–2; procarbazine 100 mg/m^2/day days 1–5; bleomycin 4 mg/m^2 i.v. day 1; bleomycin 4 mg/m^2 i.v. infusion days 1–5; doxorubicin 40 mg/m^2 i.v. day 1; prednisolone 60 mg/m^2 po days 1–5) was administered afterwards. The dose of vincristine was limited to a maximum of 2.0 mg. Radiation therapy was added after chemotherapy in the localized nasal NTCL at the physician's discretion. Second-line chemotherapy was also administered to patients who were refractory or relapsed after the initial chemotherapy.

Response and survival analysis

Tumor response was assessed using the WHO criteria. The Kaplan–Meier method was used to calculate disease-free survival (DFS) and overall survival (OS). Disease-free survival was measured from the date of the first remission to the date of the first relapse or the last follow-up. Overall survival was measured from the date of diagnosis to the date of death, from any cause, or the last follow-up visit. The χ^2-test was used to compare complete remission (CR) rate and a two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

From January 1995 to July 2000, 59 patients had received anthracycline-based chemotherapy as the initial treatment (CHOP: 31, COPBLAM-V: 28) and were included into this study. The characteristics of the patients are listed in Table 1 and it shows that the COPBLAM-V group had a poorer performance status, more advanced stage disease and a higher International Prognostic Index (IPI). B symptoms were present in 21 patients (35.6%) and hemophagocytosis was documented in only 3 patients. Patients with extranasal NTCL had skin (7), liver (3) and small bowel lesions (4) without involvement of the upper aerodigestive tract. CD56 and cytoplasmic CD3 were positive in 86.8% and 96.1%, respectively. *In situ* hybridization to EBER 1/2 was checked in 34 patients and positive in 23 patients (67.6%).

Outcomes of anthracycline-based combination chemotherapy

After the initial anthracycline-based chemotherapy, 21 patients achieved CR (CR rate: 21/59 = 35.6%) and 6 patients had a partial response (PR). Detailed results are summarized in Table 2. Of the 27 patients who had initially responded to chemotherapy, 15 patients relapsed later (locoregional relapse: 9, systemic relapse: 6). The temporal relationship between the cumulative incidence rate of locoregional relapse and systemic relapse is shown in Fig. 1. The median time to relapse was 3.0 months. In Fig. 2A it is also shown that the median DFS of 21 patients in CR was 10.1 months (2-year DFS: 22.9%). Twenty-eight patients were given additional radiotherapy after chemotherapy.

After a median follow-up of 27.2 months (range: 5.4–71.9 months), 33 patients died and the median OS was 19.6 months (2-year OS: 44.2%) (Fig. 2B). Causes of death were disease progression in 24 patients, treatment-related complications in 5, other diseases in 1 and unknown causes in 3.

Analysis of factors influencing responsiveness to chemotherapy

To identify the factors affecting the responsiveness to chemotherapy, a χ^2-test on CR rate was performed with respect to age, performance status, stage, LDH level, primary site, IPI and chemotherapy regimen. The results are shown in Table 3. IPI was identified as a significant prognostic factor of CR rate.

DISCUSSION

In this study, the anthracycline-based chemotherapy produced a CR rate of 35.6%, a median DFS of 10.1 months and a median OS of 19.6 months. These results were somewhat superior to those of previous reports (13–15), but still inferior to the results of the anthracycline-based regimen in diffuse large B-cell lymphoma.

This refractoriness to anthracycline could be explained in part by the observation that CD56-positive lymphoma is highly associated with the expression of the multi-drug resistance gene (P-glycoprotein/MDR1) (16, 17). However, clinical factors affecting the responsiveness to chemotherapy have not been known until now so that it is difficult to

Table 1

Patient characteristics

Characteristics	Total	CHOP	COPBLAM-V	p-value
Sex				
Male	39	20	19	1.000
Female	20	11	9	
Age (years)				
Mean	47.8	50.4	45.0	0.114
ECOG performance status				
0,1	53	31	22	0.008
≥ 2	6	0	6	
Ann Arbor Stage				
I/II	41	27	14	0.004
III/IV	18	4	14	
LDH (IU/L)				
Mean	305.9	250.0	363.9	0.056
Primary site				
Nasal	45	26	19	0.221
Extranasal	14	5	9	
IPI				
0,1	34	23	11	0.006
2	12	6	6	
≥ 3	13	2	11	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH = lactose dehydrogenase; IPI = International Prognostic Index.

Table 2

Response to anthracycline-based chemotherapy

	CHOP	COPBLAM-V	Overall
Complete remission	12	9	21
Partial remission	4	2	6
Stable disease	6	8	14
Progressive disease	9	9	18

predict the results of chemotherapy clinically. This study showed that the CR rate was determined by IPI.

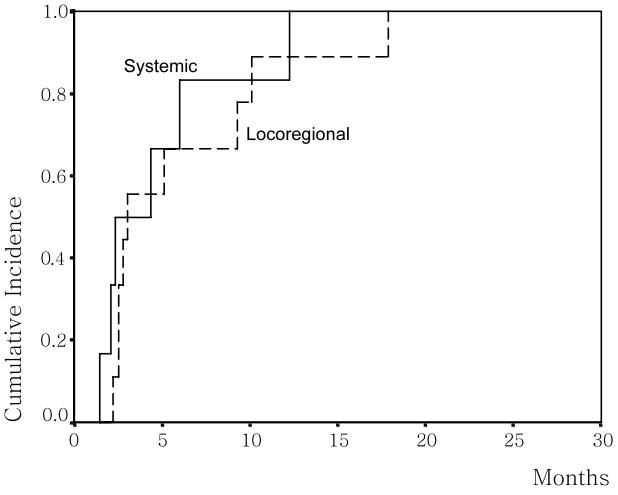

Fig. 1. Cumulative incidence rate of locoregional relapse and systemic relapse.

In stage I/II nasal NTCL, radiotherapy alone is initially effective but final outcome is unsatisfactory because of frequent systemic progression or relapse (CR rate: 60 ~ 70%, 5-year OS: 40 ~ 60%) (7–12). It has therefore been suggested that systemic treatment should be combined with radiation in localized nasal NTCL and some researchers have reported promising results with radiotherapy followed by combination chemotherapy (5-year OS: 75 ~ 87%) (18, 19). Our study showed that anthracycline-based chemotherapy as first-line treatment produced a CR rate of 43.2% and a 2-year OS of 53.1% in stage I/II nasal NTCL.

Among 16 patients who achieved CR after chemotherapy in stage I/II nasal NTCL, 8 patients subsequently received adjuvant radiation and the remaining 8 did not. DFS and OS were not significantly different in the radiation group and in the non-treated arm. This result suggests that adjuvant radiation after chemotherapy does not improve the outcome of treatment and also agrees with the results of recent randomized studies concerning aggressive lymphomas (20–22).

For systemic diseases, such as extranasal or stage III/IV nasal NTCL, combination chemotherapy is considered as the treatment of choice, but the results are generally poor (5). The outcome of first-line chemotherapy in the present analysis was also disappointing.

In conclusion, this study showed that anthracycline-based chemotherapy was unsatisfactory in terms of therapeutic outcome. A patient with a high IPI is expected to respond poorly to chemotherapy, so that innovative therapy needs to be performed.

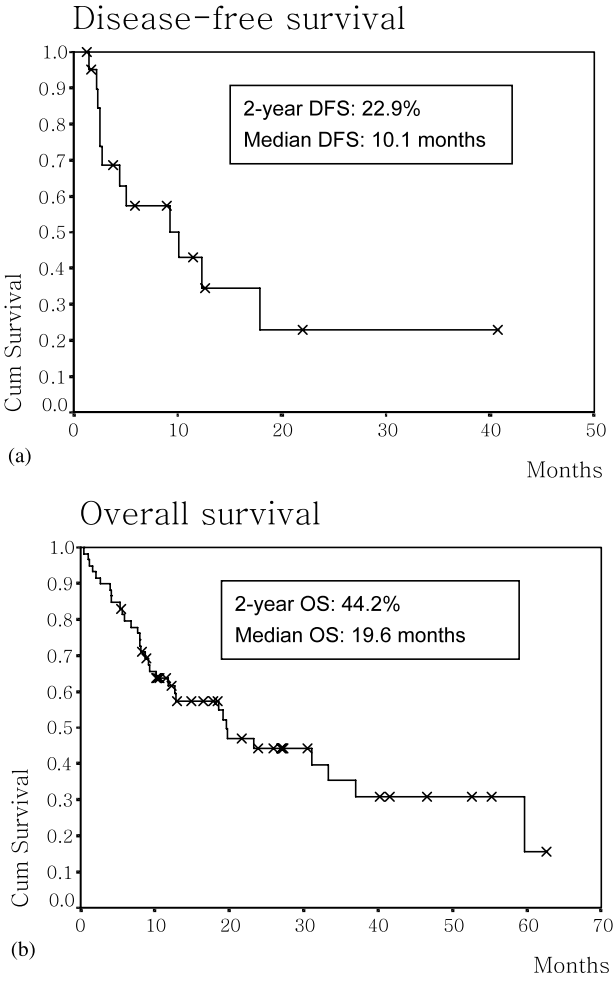

Fig. 2. Disease-free survival (A) and overall survival (B) for patients treated with anthracycline-based chemotherapy.

Table 3

Factors influencing the responsiveness to chemotherapy

		N	CR (%)	p-value
Age	≤60	48	39.6	0.110
	>60	11	18.2	
ECOG				
Performance	0–1	53	37.7	0.566
Status	2–4	6	16.7	
Stage	I/II	41	43.9	0.124
	III/IV	18	16.7	
Primary site	Nasal	45	37.8	0.745
	Extranasal	14	28.6	
LDH	Normal	30	43.3	0.265
	>Normal	25	28.0	
IPI	0–1	34	50.0	0.013
	2–5	25	16.0	
Chemotherapy regimen	CHOP	31	38.7	0.586
	COPBLAM-V	28	32.1	

Abbreviations: LDH = lactose dehydrogenase; IPI = International Prognostic Index.

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