Clinical Features of Testicular Non-Hodgkin's Lymphoma

Focus on Treatment Strategy

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Testicular primary non-Hodgkin's lymphoma (NHL) is said to account for about 5% of all testicular tumors and about 2% of extranodular lymphoma. From a clinical standpoint, we reviewed testicular NHL of stage IE treated at our department over the past 18 years. Among the 865 cases of NHL, 19 (2.2%) were primary testicular NHL, stage IE. The 19 patients had a median age of 62 years (range 48–77 years), all had diffuse B-cell lymphoma. Of the 19 patients, 8 were treated with radiotherapy after high inguinal orchiectomy (Group I), 4 received both postoperative radiotherapy and chemotherapy (Group II), and 7 received additional prophylactic intrathecal chemotherapy (Group III). The 5-year survival rates for Groups I, II and III were 37.5%, 50%, and 100%, respectively. None of the patients receiving prophylactic intrathecal chemotherapy had relapse in the central nervous system and all of them are alive and disease-free. Primary testicular NHL is relatively common among elderly persons, and many patients die as a result of central nervous system recurrence. These results suggest that preventive measures for central nervous system recurrence such as intrathecal injection of anticancer agents should be taken into consideration as early as at the induction of remission.

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Primary testicular non-Hodgkin's lymphoma (NHL) has been reported to account for 4–8% of all testicular tumors, 0.89% of all malignant lymphoma, and about 2% of extranodular lymphoma (1). Primary testicular tumors mainly occur in younger persons. In patients over 40 years of age, about 60–80% have NHL. In general, the prognosis is poor with a recurrence rate of nearly 60% (2). In the present study, we reviewed 19 patients with primary testicular NHL (stage IE) to assess clinical features and treatment protocols. We discuss the appropriate treatment based on our experience and published reports.

MATERIAL AND METHODS

Patients' characteristics

This study included 19 patients who were treated for primary testicular NHL at the First Department of Internal Medicine, Toho University School of Medicine during the 18-year period from 1979 to 1997. The 19 patients accounted for 2.2% of all patients with NHL treated during the same period. All of them had a painless tumor of the testis. None of them had fever, weight loss, or night sweats. The tumor occurred in the right testis in 14 of the 19 patients, and in the left in 5, with right-sided predominance. The median age of the patients was 62 years (range 48–77 years). The diagnosis was established from specimens obtained by orchiectomy. The diagnosis was based on orchiectomy findings in all patients. Serum HCG and α-fetoprotein were normal and the testis was examined ultrasonographically. Clinical staging using the Ann Arbor classification (3) was performed. Each patient was evaluated by history and physical examination, complete blood cell count, and blood chemistries, chest x-ray, gallium-67 scanning, bone marrow biopsy and/or aspiration, and gastrointestinal series, thoracic and abdominal computed tomography (CT) scanning. All patients were in stage IE in this study.

The histological classification was evaluated according to the Working Formulation (4). In all patients, immunohistochemical studies were also performed on paraffin-embedded sections: the avidin-biotin antibodies (L26, MB1, LN1, MT1, and UCHL1). Of the 19 testicular lymphomas, 16 were of diffuse large cell type and 3 were of diffuse mixed cell type. Immunohistochemical studies of 19 lymphomas revealed that all of them were of the B-cell type. According to the WHO classification, the performance status was 0 or 1 in 18 patients and 2 in one

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patient. The lactate dehydrogenase (LDH) level exceeded the normal range in 3 patients, and the soluble interleukin-2 receptor level was 500 U/ml or higher in 3 patients. In addition, the lymphoma had extended into the epididymis in 3 patients and into the spermatic cord in 5 patients.

Treatment

Of the 19 patients, 8 were treated with radiotherapy following high inguinal orchiectomy (Group I). The radiation field involved also contralateral testis. The dose of radiation was 30 Gy in 4 patients and 40 Gy in 4. Another 4 patients received four courses of the CHOP chemotherapy regimen (cyclophosphamide (CPM) 750 mg/m^2, doxorubicin (DXR) 50 mg/m^2, and vincristine (VCR) 1.4 mg/m^2 on day 1, and prednisolone (PDN) 60 mg/m^2 on days 1–5) as well as high inguinal orchiectomy and postoperative radiotherapy (Group II). Another seven patients (Group III) received postoperative radiotherapy and 4 courses of the COP-BLAM regimen (CPM 500 mg/m^2, DXR 50 mg/m^2, and VCR 1.4 mg/m^2 on day 1, bleomycin 10 mg on day 10, and procarbazine 100 mg/m^2 and PDN 40 mg/m^2 on days 1–10). For prevention of recurrence in the central nervous system, they also received intrathecal injections of Ara C (20 mg), methotrexate (15 mg), and PDN (20 mg) once a week for three weeks.

Determinate survival and event-free survival (EFS) rates were calculated from the date of commencement of the first treatment, using the Kaplan-Meier method. Determinate survival is defined as being due to conditions clearly unrelated to lymphoma or its treatment.

RESULTS

Complete remission (CR) was achieved in 16 of the 19 patients: 6 (75%) of the 8 patients in Group I, 3 (75%) of the 4 patients in Group II, and all 7 patients (100%) in Group III. The overall 5-year survival rate was 59.1%, with a 5-year EFS of 56.7% (Fig. 1). The 5-year survival rate and 5-year EFS were 37.5% and 47.2%, respectively, for Group I, 50% and 64.2% for Group II, and 100% and 100% for Group III. There were no significant differences in these rates among the three groups, possibly because the

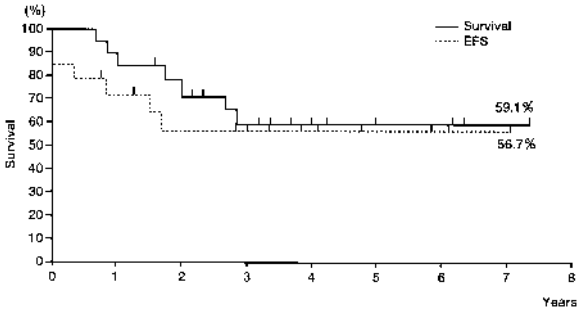

Fig. 1. Overall survival and event-free survival with primary testicular lymphona.

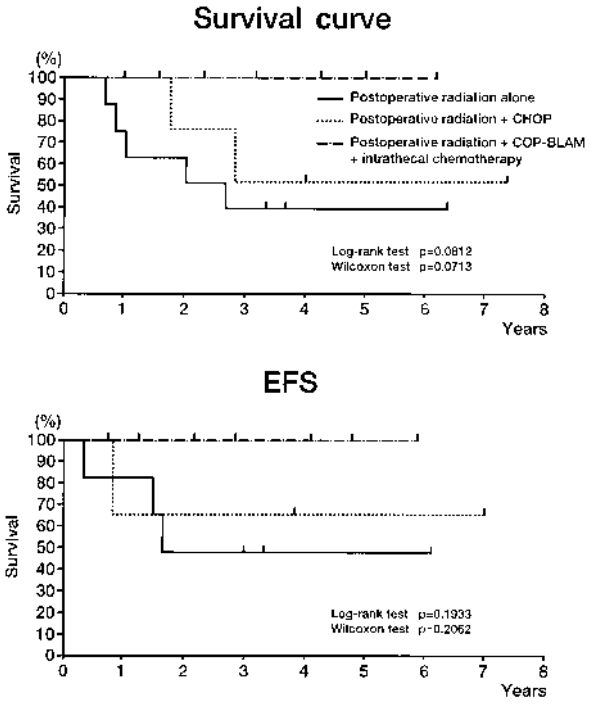

Fig. 2. Survival curve and EFS.

number of patients was too small (Fig. 2). NHL did not recur in the central nervous system in any of the patients who received prophylactic intrathecal therapy. All the patients are still alive and without disease. Adverse reactions of grade 3 or higher included granulocytopenia in 3 patients and peripheral neuropathy in 2. These adverse reactions were treated with G-CSF and other agents given during chemotherapy and they did not lead to discontinuation of chemotherapy. This prophylactic therapy did not cause serious toxicity and was considered safe even for elderly patients. The disease recurred in 4 of the 16 patients who had achieved CR. Of these four patients, three died. Recurrence occurred in the central nervous system in all 3 patients. Despite treatment with chemotherapy, radiotherapy, and intrathecal injection of anticancer agents after relapse, the three died after 4 to 14 months. In one patient who had recurrence in the opposite testis, CR was achieved again by radiotherapy and chemotherapy. He is alive at present.

DISCUSSION

Primary testicular NHL was first reported in 1877 by Malassez (5). This malignancy is a relatively rare disease which principally occurs in middle-aged or older men. It spreads through the blood and lymphatic vessels as well as the ductus deferens to the epididymis, leading to rapid progression to systemic spread. Consequently, it is quite rare for the disease to be at stage IE when detected. There are therefore only a few reports on series of patients with primary testicular NHL of stage IE and the best treatment

Table 1

Reported treatment results in primary testicular lymphoma

	No. of patients	Stage	Treatment	Complete remission	5-year survival (%)	Sites of extranodal and nodal disease at relapse					
						CNS	Testis	Lung	Skin	Waldeyer's	Nodal
Duncan (1980)	24	I∼IV	O+RT	20/24	64 (stage I·II) 17 (stage III·IV)	3/20	2/20	2/20	1/20	5/20	3/20
Read (1981)	51	I∼IV	O+RT (+CT)	NA	20	5/51	NA	5/51	9/51		
Buskirk (1982)	17	I∼IV	O+RT	16/17	73 (stage I) 25 (stage II)	2/11	1/11	2/11	1/11	5/11	3/11
Tepperman (1982)	16	I∼IV	O+RT (+CT)	7/16	Median 9.5 months	4/8		2/8	1/8		5/8
Connors (1988)	14	I·II	O+RT	100%	50	1/7	3/7	3/7		1/7	2/7
	15	I·II	O+RT+CT	100%	93						1/1
Martenson (1988)	30	I∼IV	O+RT (+CT)	NA	40.2	6/20	4/20	5/20	1/20	2/20	8/20
Roche (1989)	9	I	O+RT (+CT)	5/9	74	1/4	2/4		1/4		3/4
Crellin (1993)	34	I∼IV	O+CT	50%	38.7	6/6	2/6	3/6	1/6	3/6	NA
Touroutoglou (1995)	22	I∼IV	O+RT+CT	16/22	50	9/22	7/22				
Ostronoff (1995)	16	I·II	O+RT+CT	16/16	Median 45 months	8/16	1/16	2/16	1/16		
Sasai (1996)	8	I∼IV	O+RT+CT	7/8	45	3/7	1/7		1/7		2/7
Niitsu (1997)	19	I	O+RT	6/8	37.5	2/3	1/3				
			O+RT+CT	3/4	50	1/1					
			O+RT+CT+IT	7/7	100						

O = orchiectomy; RT = radiation therapy; CT = chemotherapy; IT = intrathecal chemotherapy; NA = not available.

for this stage has not yet been established. However, there is an urgent need for reliable therapy for this condition.

High inguinal orchiectomy alone was previously performed to treat stage IE primary NHL of the testis, but the 5-year survival rate was as low as 12% and most patients died within 2 years after systemic dissemination (6). Postoperative radiotherapy was introduced in the 1980s, leading to a rise in the 5-year survival rate to 50–70%. However, the rate was still lower than that for extranodular lymphoma at sites other than the testis (80–95%) (7, 8). Subsequently, it was reported that the use of combination chemotherapy achieved a 4-year rate of 93% (9). Because many patients with this disease are elderly, however, they generally find it difficult to tolerate potent chemotherapy. In the present study, the 5-year survival rate was 37.5% for patients receiving postoperative radiotherapy alone, 50% for patients receiving chemotherapy after postoperative radiotherapy, and 100% for patients receiving chemotherapy and intrathecal injection of anticancer agents after postoperative radiotherapy. As shown in Table 1, central nervous system recurrence occurred in most cases. According to Connors et al. (9), the combination of chemotherapy and radiotherapy alone failed to prevent central nervous system recurrence in several patients. This indicates that micrometastasis in the central nervous system cannot be prevented by chemotherapy alone because drugs administered systemically do not effectively cross the blood–brain barrier (7).

Tourouroglou et al. (10) and Ostronoff et al. (11), respectively, reported CNS recurrence in 40.9% and 50% of patients receiving chemotherapy or radiotherapy alone.

Our analysis also showed that central nervous system recurrence occurred in some of the patients treated with postoperative radiotherapy alone or radiotherapy plus systemic chemotherapy. In patients receiving additional prophylactic intrathecal injection of anticancer agents, recurrence was completely prevented. From these results we conclude that not only radiotherapy and chemotherapy, but also the prophylactic intrathecal therapy should be incorporated into standard protocols for primary testicular NHL. Because none of the patients receiving prophylactic intrathecal therapy had any severe adverse events, it is considered to be safe for elderly patients. CNS prophylaxis should be given during or after chemotherapy because the disease recurred in the CNS during radiotherapy in some patients.

Contralateral recurrence of primary testicular NHL has been reported to occur in 0–30% (12, 13). Like the central nervous system, the contralateral testis is considered to be a sanctuary site. In other words, there is a blood–testis barrier which drugs administered systemically cannot cross (14). Tepperman et al. (15) reported that contralateral radiotherapy succeeded in preventing contralateral recurrence. In the present study, no contralateral recurrence occurred in patients who received prophylactic radiotherapy for the contralateral testis.

These findings show that standard treatment protocols for primary testicular NHL should include chemotherapy with prophylactic intrathecal therapy and contralateral postoperative irradiation, even if the tumor is stage IE.

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