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Combined Chemotherapy and Radiotherapy for Malignant Lymphomas of the Head and Neck

(chemotherapy/radiotherapy/malignant lymphomas)

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Sixty-three of the patients treated for malignant lymphoma, and diagnosed as being cases of reticulum cell sarcoma were divided into 2 groups to assess the effects of chemotherapy. Group 1 was given VER (vincristine, cyclophosphamide (Endoxan) and betamethasone (Rinderon) and radiation, while Group 2 single agent and radiation.

The 5-year survival rates showed a significant differences of 69% vs. 44%, respectively.

In terms of side-effects, the so-used combined therapy had few serious side-effects compared with other types of combined chemotherapy.

We hold the view that chemotherapy should be administered in combination with radiation, even during stages I and II.

Various studies on the relationship between the pathological classification and prognosis have been conducted with reference to non-Hodgkin's lymphomas.

Regarding the therapeutic principles, no agreement has been reached as to whether chemotherapy should be used in combination with radiotherapy.

We compared the results obtained with a new therapeutic program of our design with the results based on an older program (1).

MATERIALS AND METHODS

Of all the patients with malignant lymphoma treated at the Department of Oto-Laryngology, Tottori University from June, 1965 to March, 1979, 63 were diagnosed as having reticulum cell sarcoma.

In this series, there were 36 men and 27 women with malignant lymphoma (M : F = 1.3 : 1). Ages ranged was from 21–81 years.

These patients were divided into two groups, namely, group A consisting of patients treated from June, 1965 to April, 1973 (36 cases) and group B comprising those treated thereafter (27 cases).

The primary sites of the sarcoma in these two groups are shown in Table I.

Classification of the clinical staging was made in accordance with the form prepared at the Ann Arbor Conference (1971) (2).

In the group A, however, the clinical staging was classified retrospectively, on the basis of clinical findings and radiologic findings without lymphography.

TABLE I. *Incidence of Primary Sites*

Site	Group		Total
	A	B	
Palatine tonsil	19	13	32
Epipharynx	4	5	9
Lingual tonsil	3	1	4
Parapharynx	0	1	1
Nasal cavity	5	2	7
Maxillary sinus	5	2	7
Ethmoidal sinus	0	1	1
Frontal sinus	0	1	1
Submandibular lymph node	0	1	1
Total	36	27	63

Therapies adopted for stages I and II, the localized type, are as follows.

In the group A, external irradiation of ^{60}Co (4000 R or more) was administered mainly and a single agent (cyclophosphamide 2500 mg or Mitomycin C 40 mg or more) was given simultaneously, with or after irradiation in the most cases.

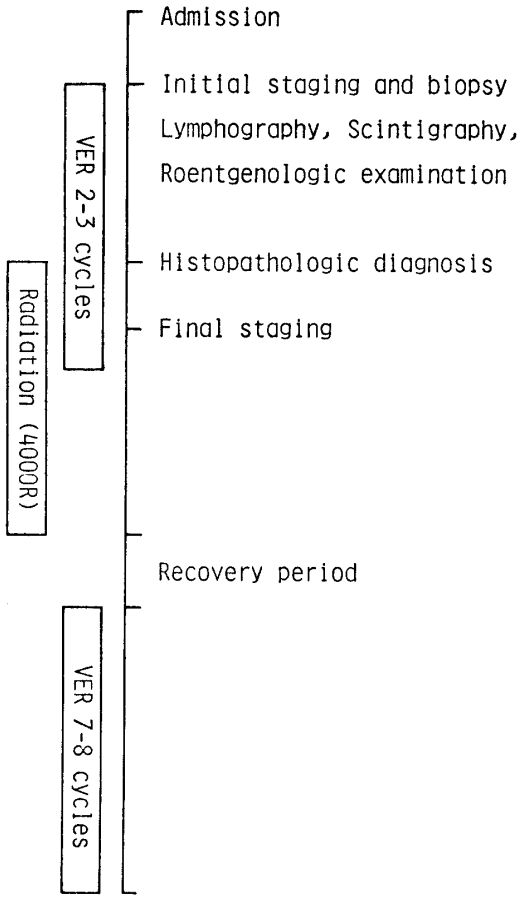

Fig. 1. Therapeutic course for stages I and II of lymphomas of the head and neck.

In group B, biopsy was taken from the primary lesion after a gross assessment of the clinical staging.

Simultaneously with exploratory excision, chemotherapy (with vincristine 1 mg i. v. once weekly, cyclophosphamide (Endoxan) 500 mg i. v. once weekly and betamethasone (Rinderon) 4 mg i. m. twice weekly, as 1 cycle of the VER program) was initiated and thereafter, 2 to 3 cycles of this program were administered. During this period, the final staging was assessed by lymphography, scintigraphy, X-ray examination and endoscopy.

As soon as the pathological diagnosis was obtained, radiotherapy was started, the total dose being fixed at 4000 R.

After the completion of radiotherapy, general conditions were examined and chemotherapy was resumed for a total of 10 cycles (Fig. 1).

A weekly schedule, as shown in Table II, was drawn up since there the side-effects, particularly bone marrow depression during the therapy had to be monitored.

TABLE II. *Weekly Schedule*

Mon.	Blood count and urine test (weekly) Chest X-ray, liver and renal function tests (every other week)
Tue.	Vincristine 1mg i. v. infusion Rinderon 4mg i. m.
Wed.	
Thu.	
Fri.	Endoxan 500mg i. v. infusion Rinderon 4mg i. m.
Sat.	
Sun.	

For stages III and IV, the generalized type, the therapy consisted mainly of chemotherapy administered repeatedly in a unit of 10 cycles and dependent on the individual status.

The interval of administration was set at about one month.

Radiation in doses of 1000—2000 R was concomitantly administered only when the patients had severe pain.

RESULTS

Therapeutic results in the two groups are presented in Table III.

TABLE III. *Survival Rates according to Groups*

Survival	Group		Total
	A	B	
5 yr	16/36(44.4%)	9/13(69.2%)	25/49(51.0%)
3 yr	18/36(50.0%)	19/24(79.2%)	37/60(61.7%)

Improvement in results was clearly evident in group B. The results were studied with reference to factors which may possibly affect prognosis.

Table IV shows the survival rates, according to the primary site.

TABLE IV. *Survival Rates according to Primary Sites*

Site		Group A	Group B	Total
Palatine tonsil	5yr	11/19(57.9%)	5/ 7(71.4%)	16/26(61.5%)
	3yr	12/19(63.2%)	8/11(72.7%)	20/30(66.7%)
Epipharynx	5yr	3/ 4(75.0%)	1/ 1(100%)	4/ 5(80.0%)
	3yr	3/ 4(〃)	4/ 4(〃)	7/ 8(87.5%)
Lingual tonsil	5yr	0/ 3		0/ 3
	3yr	0/ 3	0/ 1	0/ 4
Parapharynx	5yr		1/ 1(100%)	1/ 1(100%)
	3yr		1/ 1(〃)	1/ 1(〃)
Nasal cavity	5yr	1/ 5(20.0%)	1/ 2(50.0%)	2/ 7(28.6%)
	3yr	1/ 5(〃)	2/ 2(100%)	3/ 7(42.9%)
Maxillary sinus	5yr	1/ 5(20.0%)	1/ 1(100%)	2/ 6(33.3%)
	3yr	2/ 5(40.0%)	2/ 2(〃)	4/ 7(57.1%)
Ethmoidal sinus	5yr			
	3yr		1/ 1(100%)	1/ 1(100%)
Frontal sinus	5yr		0/ 1	0/ 1
	3yr		0/ 1	0/ 1
Submandibular lymph node	5yr			
	3yr		1/ 1(100%)	1/ 1(100%)

The 5-year survival rate was 58.8% (20/34) in the cases of malignancy in Waldeyer's region and 30.8% (4/13) in cases of nasal and paranasal regions. The prognosis was good in the case of primary lesions in the palatine tonsil and epipharynx.

Survival rates according to age are shown in Table V.

TABLE V. *Survival Rates according to Age*

Years		Group A	Group B	Total
21 – 40	5yr	2/ 7	0/ 1	2/ 8(25%)
	3yr	2/ 7	1/ 3	3/10(30%)
41 – 60	5yr	9/16	8/ 9	17/25(68%)
	3yr	10/16	13/13	23/29(79.3%)
61 –	5yr	5/13	3/ 3	8/16(50%)
	3yr	5/13	6/ 8	11/21(52.4%)

Prognosis for patients under 40 years of age was particulary poor.

In those 41—60 years of age, the survival rate was 68%, and the results in

group B were excellent.

Table VI shows survival rates according to clinical staging.

TABLE VI. *Survival Rates according to Clinical Staging*

Stage		Group A	Group B	Total
I	5yr	7/13	3/ 4	10/17(58.8%)
	3yr	8/13	8/ 8	16/21(76.2%)
II	5yr	8/18	6/ 8	14/26(53.8%)
	3yr	9/18	8/11	17/29(58.6%)
III	5yr	1/ 4		1/ 4(25%)
	3yr	1/ 4	3/ 4	4/ 8(50%)
IV	5yr	0/ 1	0/ 1	0/ 2
	3yr	0/ 1	0/ 1	0/ 2

When a comparison was made of stages I and II, there was a significant difference between group A with 48.4% (15/31) and group B with 75% (9/12).

The relationship between the number of days required from exploratory excision to initiation of the treatment and prognosis is shown in Table VII.

TABLE VII. *Survival Rates according to Initiation of Treatment from Exploratory Excision*

Days		Group A	Group B	Total
0 – 14	5yr	9/22	4/ 5	13/27(48.1%)
	3yr	10/22	11/12	21/34(61.8%)
15 – 28	5yr	5/ 9	4/ 5	9/14(64.3%)
	3yr	6/ 9	6/ 9	12/18(66.7%)
29 –	5yr	2/ 5	1/ 3	3/ 8(37.5%)
	3yr	2/ 5	2/ 3	4/ 8(50%)

On the whole, the relationship was not clear except in cases in which the initiation of the treatment was delayed for a month or longer.

When a comparison was made in cases where the treatment was started within two weeks, there was a considerable difference between the two groups, with 40.9% (9/22) vs. 80% (4/5).

TABLE VIII. *Survival Rates according to Frequency of Biopsy*

Frequency		Group A	Group B	Total
1	5yr	14/27	8/10	22/37(59.5%)
	3yr	15/27	15/19	30/46(65.2%)
over 2	5yr	2/ 9	1/ 3	2/12(25%)
	3yr	3/ 9	4/ 5	7/14(50%)

Table VIII shows the relationship between the frequency of exploratory excision and the prognosis.

The higher the frequency, the poorer was the prognosis, however, the results in group B were superior in the case of one exploratory excision.

Of the 27 subjected to the VER program, nine (33.7%) had side-effects and the remaining 18 (66.7%) had no side-effects.

In four, there was a leukopenia (3000/mm^3 or less), but all recovered following withdrawal of irradiation for about one week.

Mild hepatic disorder occurred in two, but we were able to complete the program by administering a counteractant.

An 78 year-old woman developed candidasis but such soon disappeared with the cessation of steroids, and with oral hygiene.

In one patient, interstitial pneumonia developed, however, with steroid and antibiotic therapy and bed rest for about three months, cure was all but complete.

In one 70 year-old woman in whom the tendon reflex disappeared, the treatment was continued with the dosage of vincristine reduced by half, but she died about three months later of a cerebral metastasis.

Recurrences were observed in 26 out of 50 cases of stages I and II. Local recurrences were often seen in the nasal and paranasal regions, while recurrences in the Waldeyer's cases were noted in the non-irradiated organs.

The interval of recurrences is shown in Table IX.

TABLE IX. *Interval of Recurrences*

Interval (yr)	Stage		Total
	I	II	
~ 0.5	8	7	15(57.7%)
~ 1	1	2	3(11.6%)
~ 2	1	2	3(11.6%)
~ 3	0	1	1(3.8%)
over 4	2	2	4(15.4%)
	12	14	26

The rate of recurrence was in 69.2% within one year and in 80.8% within two years.

Exceptionally, there were four cases of late recurrence in the Waldeyer's region (palatine tonsil 3 cases, epipharynx 1 case), the interval being 4 years in 2 cases, 5 years in 1 case and 7 years in 1 case.

DISCUSSION

The term "reticulum cell sarcoma" is not histogenetically appropriate.

As the new classification has not been established and generalized clinicopathologically, we divided patients with reticulum cell sarcoma treated during

the past 15 years, into two groups, for a comparative study.

We designed the VER program because :

1) Reticulum cell sarcoma follows various clinical courses.

Pathologically, much remains to be determined and there is no agreement as to whether this tumor is monocentric or multicentric.

2) Radiotherapy for stages I and II and a method consisting mainly of chemotherapy for stages III and IV have hitherto been prescribed.

Recently, adjuvant chemotherapy has been prescribed for stages I and II, but there are differences of opinion regarding the combined use of chemotherapy and radiotherapy, because of the related side-effects.

Our method was designed to limit the number and grade of side-effects and to achieve the local and general therapeutic effects.

3) Local recurrence rarely was seen in the irradiated field, rather such occurred in other organs.

The regimen resembles the COP program (vincristine 2 mg, cyclophosphamide 800 mg/m^2 and prednisone 60 mg/m^2) designed by Luce *et al.* (3) but differs in that the doses of vincristine and cyclophosphamide were reduced in consideration of the combined application of radiation and also because a steroid was administered intermittently in an attempt to inhibit side-effects.

When a comparison was made of the therapeutic results in these two groups, considerable improvement in the results was observed in group B, with the survival rate being 44.4% for group A and 69.2% for group B.

These results are comparable to data published elsewhere including results (50%) recently by Ono (4) at the National Cancer Center.

A comparative study was also made of the factors which could possibly affect the prognosis.

When the relationship between the primary site, age, clinical stage, the number of days from exploratory excision to initiation of the treatment and frequency of biopsy on the one hand and prognosis on the other was examined, the results with the group B were superior to those with group A, in each parameter.

Particularly, in the case of Waldeyer's region, the results were superior, as compared to the results of Al-Saleem *et al.* (38.1%) (5), Banfi *et al.* (41.9%) (6) and Saito *et al.* (35.2%) (7) who administered therapy consisting mainly of radiation.

Survival rates according to the frequency of biopsy are shown in Table VIII.

When there are findings of gangrenous rhinitis, the confirmation of a histopathological diagnosis may be delayed and findings of chronic inflammation are obtained in many cases. Consequently, the frequency of exploratory excision increases, and to some extent accounts for the poor prognosis.

In such a case, a step similar to one adopted for the generalized type should be taken even when the case is classified as stage I.

Since the incidence of late recurrence and double cancer may increase, a follow-up observation every 6 months is recommended, even after a lapse of

five years.

As for the treatment of a recurrence, the MOPP program (8) and VEMP program (9) are also available when combined chemotherapy is being considered.

Our program consists of the VER program plus procarbazine 100 mg/day orally and differs from the regimen reported by others (10).

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