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Abstract

By endolymphatic injection of radioisotope ¹³¹I.Lipiodol, so.called endolymphatic radiotherapy, we treated 10 cases with malignant lymphoma and found a marked tumor reduction to normal size in all the 10 cases we tried. It seems that this method is one of the most effective therapeutic methods for malignant lymphoma, espe. cially invading into the retroperitoneal lymph nodes.

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CLINICAL EVALUATION OF ENDOLYMPHATIC RADIOTHERAPY IN MALIGNANT LYMPHOMA

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Abstract: By endolymphatic injection of radioisotope ^{131}I -Lipiodol, so-called endolymphatic radiotherapy, we treated 10 cases with malignant lymphoma and found a marked tumor reduction to normal size in all the 10 cases we tried. It seems that this method is one of the most effective therapeutic methods for malignant lymphoma, especially invading into the retroperitoneal lymph nodes.

It was FISCHER and ZIMMERMAN (1) who first suggested a possibility of applying lymphography for the treatment, and WALLACE *et al.* (2, 3) attempted first to inject therapeutic materials into the lymph vessels for treatment.

Subsequently, there appeared many reports by CHIAPPA *et al.* (4-7) who treated malignant lymphoma and metastatic lymph nodes by injecting ^{131}I -Lipiodol into the lymphatics, the so-called endolymphatic radiotherapy. Simultaneously ARIEL (8, 9), SEITZMAN (10), BÉTOULIÈRES *et al.* (11), LIEBNER (12), zum WINKEL *et al.* (13) have reported the efficacy of this therapeutic method on malignant lymphoma. Despite these clinical studies carried out using endolymphatic isotopes, there is still controversy on the importance and limitations of this method in the treatment of malignant lymphoma. In addition, there is as yet no report on study concerning this therapy in Japan.

In our experimental study on dogs, we reported that this method had little side-effect and it showed the irradiation effect selectively on lymph nodes (14). Since then we have applied this therapeutic method to patients with malignant lymphoma and observed a marked reduction of tumors in all the cases we treated. Here we present our clinical results.

PATIENTS AND METHODS

The patients on whom endolymphatic radiotherapy was attempted were 10 cases as shown in Table 1; consisted of 3 cases of Hodgkin's disease, 4 reticulum cell sarcomas, one lymphosarcoma and two chronic lymphatic leukemia. The isotope used was intralymphatic injection iodinated triolein ^{131}I in Lipiodol U.-F. (a product of the Radiochemical Center, England and abbreviated as ^{131}I -Lipiodol in this report). To each case 4.5 ml ^{131}I -Lipiodol con-

TABLE 1 PATIENTS TREATED WITH ENDOLYMPHATIC RADIOTHERAPY

Case	Sex	Age	Histological diagnosis*	Dead or alive**	Survival time			
					After the onset		After ¹³¹ I administration	
					Years	Months	Years	Months
1	M	55	RCS	dead	2	1	1	3
2	M	33	CLL	alive	5	10	3	4
3	M	39	RCS	dead		10		7
4	M	51	Hodgkin	dead		9		9
5	M	49	Hodgkin	alive	5		2	8
6	M	28	Hodgkin	alive	4	9	2	6
7	M	42	CLL	alive	3	1	2	11
8	M	68	RCS	alive	1	11	1	3
9	M	68	LS	dead	2			1
10	M	24	RCS	dead		6		

* RCS: Reticulum Cell Sarcoma

CLL: Chronic Lymphatic Leukemia

LS: Lymphosarcoma

** on the 31 March, 1973

taining specific radioactivity of 10 mCi/ml was used. The total volume of ¹³¹I-Lipiodol on each side was adjusted before injection to 7-10 ml by mixing with Lipiodol Ultrafluide not containing isotope.

Following the method of KINMONTH, the mixture of 0.5 ml patent blue and an equal volume of 1-2% xylocaine was subcutaneously injected on the dorsum of both feet, then incision was made for 1.5-2 cm along the visible lymphatic stained blue to expose the lymph vessel, needle was inserted into the lymphatic and physiological saline was injected through the needle. After confirming the saline flow into the lymph vessel, isotope was simultaneously injected bilaterally into the exposed dorsal lymph vessels.

In order to limit the uptake of free ¹³¹I by the thyroid, 10 ml (50 mg) iodinated sodium solution was given orally to the patient the night before the injection.

Immediately thereafter and 24 hours after the injection periodically at intervals of about one week, abdominal and chest X-rays (anterior-posterior, lateral and oblique pictures) were taken. The plane scanning, linear scanning, and the scintillation camera were also used to detect the organ distribution of the isotope. In addition, to check the excretion of ¹³¹I into feces and urine, the amounts of ¹³¹I excreted into urine and feces were measured every two days for two weeks.

For determining of therapeutic effects, the size of lymph node was measured by planimetry on the lymphograms taken periodically after the isotope injection, and was calculated by the degree of shrinkage expressed in terms of percentage by the following formula: $\frac{A-B}{B} \times 100$ (where A: the total

area of the lymph node before the isotope injection, B: the total area of lymph node at given days after the injection); we studied the efficacy from the so-called tumor shrinkage curves, and also took the improvement of subjective symptoms and changes of humoral factors into consideration.

RESULTS

1. Effect on lymphoma with endolymphatic radiotherapy

Fig. 1 shows the results of endolymphatic radiotherapy conducted on the

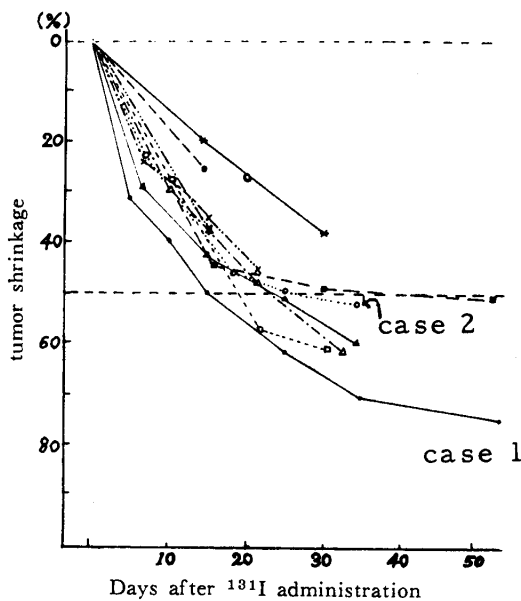


Fig. 1. The tumor shrinkage curves of patients treated with endolymphatic radiotherapy.

patients being determined by the tumor shrinkage. This was measured with lapse of time and was expressed in percentage, indicating a marked shrinkage of tumors in all the cases treated; the shrinkage of 20-50%, (35% in average) 2 weeks later and 50% in average one month later. Two representative cases are described as follows.

Case 1. A 55-year old female with main complaint of systemic lymph node swelling. Marked lymph node swellings were observed at each side of neck, the left clavicular fossa, and especially the right inguinal region reaching fist-size. By biopsy this was diagnosed as reticulum cell sarcoma. After

endolymphatic injection of 35mCi ^{131}I -Lipiodol from the dorsum of both feet, on the third day the right inguinal lymph node, which was as big as a fist, was somewhat softened and began to shrink, by one week it became clearly smaller, and within two weeks it grew as small as the tip of thumb. Fig. 2 and Fig. 3 illustrate the lymphograms taken 24 hours and one month after the ^{131}I -Lipiodol injection respectively. As shown in these lymphograms the swollen inguinal and the retroperitoneal lymph nodes are markedly reduced in sizes. Studying the case by the lymph node shrinkage curves, the rate of shrinkage is 50% by two weeks, and 60% by three weeks as shown in Fig. 1. By the scanning (Fig. 4) and the scintillation camera (Fig. 5) it is obvious that ^{131}I -Lipiodol has been distributed homogeneously to lymph nodes. By the



Fig. 2. Lymphogram taken 24 hours after administration of ^{131}I -Lipiodol (Case 1)



Fig. 3. Lymphogram taken one month later (Case 1). Note remarkable shrinkage of lymph nodes.

linear scanning conducted at intervals of 2 hours and one week after ^{131}I Lipiodol injection as shown in Fig. 6, the isotope is distributed quite densely and selectively in the inguinal and retroperitoneal lymph nodes. And it was demonstrated that the isotope is retained in the lymph nodes over a long period of time as observed in animal experiments. ^{131}I -distribution in the lung is clearly observable, but it was diminished markedly and quite rapidly. In thyroid gland its distribution was not detected by the linear or plane scanning. Treatment with Bleomycin was started on this patient 3 weeks after ^{131}I -Lipiodol injection. The superficial lymph nodes became hardly detectable, the retroperitoneal lymphogram returned practically normal, general conditions were also improved, and she was discharged after 3 months of treatment. There could be observed no marked change of peripheral blood picture and bone marrow picture, nor was there any abnormality of the thoracic X-ray picture and functions of liver and thyroid gland.

Case 2. A 33-year old male, with chief complaint of bilateral swelling of the neck. There were somewhat hard lymph nodes of a pea to a hen's egg size palpable bilaterally under the jaw, on the both sides of neck, in the clavicular fossa and in the inguinal region. There was no fusion nor severe

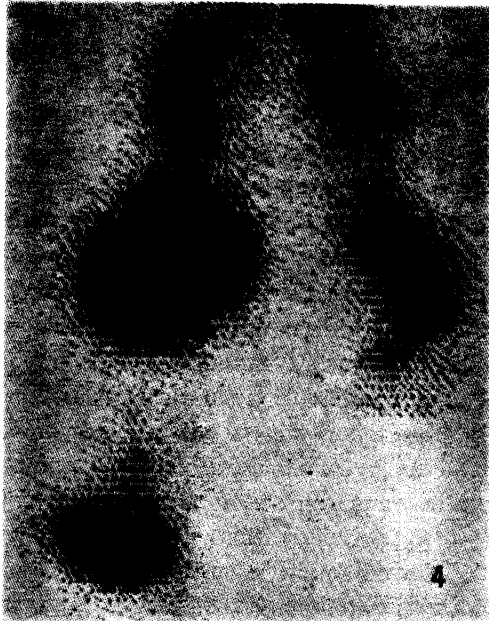


Fig. 4. Scintigram after administration of ^{131}I -Lipiodol (case 1). Note retention of the isotope throughout the pelvic and periaortic lymph nodes

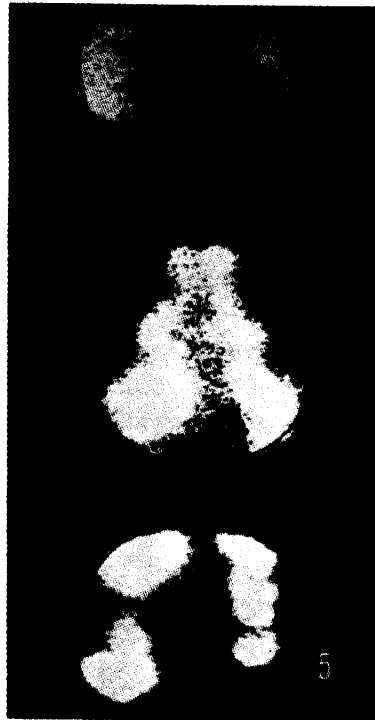


Fig. 5. Scintiscamera of Case 1. upper: chest. middle: abdomen. lower: inguinal

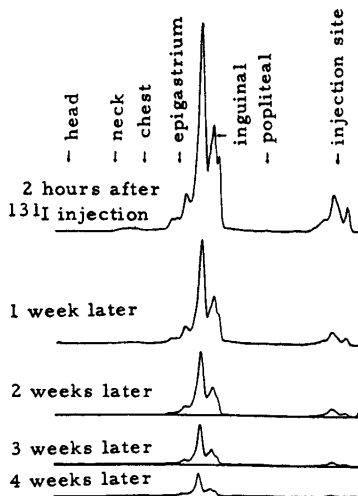


Fig. 6. Linear scan of Case 1.

pain. By biopsy and other laboratory findings this case was diagnosed as chronic lymphatic leukemia. The retroperitoneal lymph nodes revealed a moderate swelling presenting the picture characteristic of malignant lymphoma by the lymphogram with Lipiodol Ultrafluide not containing ^{131}I . The lymphograms taken periodically did not show any clear-cut shrinkage even at the termination of Bleomycin (15 mg/day, twice a week to the total of 300 mg). Therefore, the endolymphatic therapy of ^{131}I -Lipiodol was commenced, and pursued the size of lymphoma by the X-ray pictures taken with lapse of time. Three weeks

later the shrinkage was over 50% and one month later over 60%, clearly showing the improvement as in Case 1 (Fig. 1). The uptake of ^{131}I into the lymph nodes is extremely marked by scintigram or scinticamera. By the linear scanning conducted with lapse of time the ^{131}I -distribution in the inguinal and retroperitoneal lymph nodes is marked.

2. *The excretion of ^{131}I into urine and feces in the cases receiving endolymphatic radiotherapy.*

Figs. 7 and 8 show the amounts of ^{131}I excreted into urine and feces respectively. The excreted amounts vary considerably with cases; in general

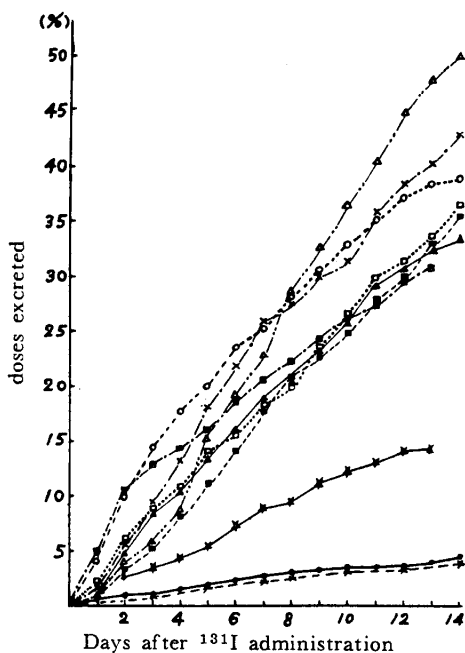


Fig. 7. Excretion of ^{131}I into urine in the patients given endolymphatic radiotherapy

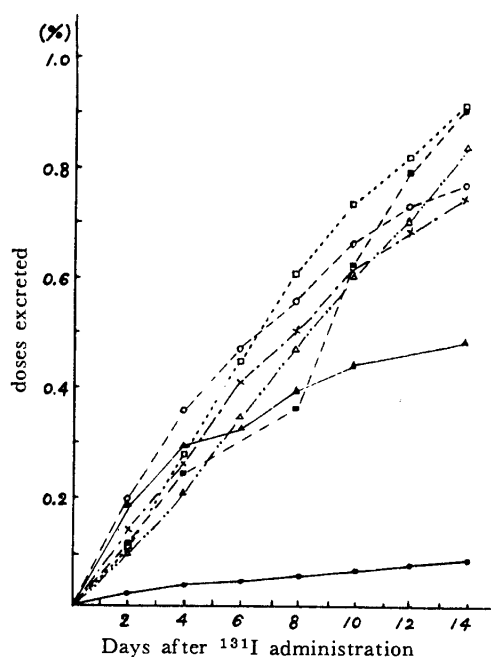


Fig. 8. Excretion of ^{131}I into feces in the patients given endolymphatic radiotherapy

the excretion into urine for two weeks was 5 to 40% showing an inverse relation to the swelling of the inguinal and retroperitoneal lymph nodes. Excretion into feces was under 1% in all the cases.

DISCUSSION

Advantages of the ^{131}I -Lipiodol injection into the lymphatics, so-called endolymphatic radiotherapy, can be pointed out as follows; 1) the treatment can be accomplished by a single injection into the lymph vessel and, if

necessary, repeated injections can be done. 2) By lymphograms, scintiscanning, and scinticamera it is possible to observe the ^{131}I -distribution in the lymph nodes. And by taking roentgenograms with lapse of time we can obtain the lymph node shrinkage curves, by which the shrinkage effect can be determined objectively. 3) As the radiation range of β -emitter from ^{131}I is about 2 mm, a strong radioactivity is directly gathered onto the pathologic focus, although it hardly gives any injurious effect on the organs around the pathological lymph nodes. 4) Other than a transient or a slight lymphocytopenia (15) there is no inhibitory effect at all on the hematopoietic organs including the bone marrow.

It has been said that in the endolymphatic injection of ^{131}I -Lipiodol from the dorsum of feet the retroperitoneal lymph nodes receive 200–800 rads (Siegel), 333–1,000 rads (Picard), 700 rads in average (Dargent, Romeiu) per 1 mCi of ^{131}I -Lipiodol (13). Therefore, for the cases with malignant lymphoma showing the lymph nodes swelling in the inguinal, iliac and retroperitoneal regions this method seems to be of the first choice. Also in our 10 cases the lymph node shrinkage was marked. Especially, Case 2, who was treated with Bleomycin 2 months prior to the ^{131}I -Lipiodol injection, showed no clear-cut shrinkage of lymph nodes. When the ^{131}I -Lipiodol treatment was given, the shrinkage of lymph nodes was observed in about the same degree as with the other cases, and this case suggested a possibility of the shrinkage effect by ^{131}I -Lipiodol even in the malignant lymphoma whereby Bleomycin alone does not induce the shrinkage.

As for side-effects, oil embolism of the lung by the contrast medium has been pointed out, but it is extremely rare to see any case raising clinical problems. ^{131}I , that has entered into the lung and has been distributed, is excreted more rapidly than in lymph nodes and cause little irradiation damage. By histological observations of the lung in animal experiments, likewise, no fibrosis nor any other injurious effects could be seen (14). And by the X-ray pictures there were no findings suggestive of fibrosis and other abnormalities. It is also reported that in 16% of the patients treated amenorrhea occurred, two cases showed disorders of liver function due to ^{131}I -Lipiodol, and hemolytic anemia occurred in one case (7). We did not, however, encounter such side effects in our cases. As obvious from the results of the 10 cases whom we treated, endolymphatic radiotherapy seems to be an extremely useful therapy for malignant lymphoma with the involvement of retroperitoneal lymph nodes as an adjunct of ordinary radiotherapy and chemotherapy.

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