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SOME CLINICAL ASPECTS OF CHEMOTHERAPY IN MALIGNANT LYMPHOMAS

YOSHIRO ITO

1st Department of Internal Medicine, Nagoya University School of Medicine
(Director: Prof. Susumu Hibino)

ABSTRACT

In the chemotherapy of cancer, leukemia and malignant lymphoma are two diseases that may be considered to respond best to this type of therapy[1)~4)]. Herein is described the chemotherapy of malignant lymphoma, based mainly on our experiences.

OBJECTS OF STUDY

A total of 117 cases of malignant lymphoma were studied. They consisted of 70 cases of lymphoreticulosarcoma and lymphosarcoma, 43 of Hodgkin's Disease, and 4 of Brill-Symmer's Disease. Cases with doubtful diagnosis were excluded.

Diagnosis was based on histological and cytological findings of materials obtained by needle biopsy or excised specimens of the lymphoma.

RESULTS

1) Regressing of tumor: A summary of the effects of chemotherapy based on tumor regression is presented in Table 1: namely, markedly effective, 22.5 % (43 cases), effective, 46.0% (88 cases), and non-effective, 31.4% (60 cases). Regression of tumor is based on clinical evidence of decrease in tumor mass by inspection and palpation of the affected lymph nodes.

The "markedly effective" cases of Table 1 are those where the tumor regressed to sizes less than the tip of the little finger, including those that failed to be palpated. The "effective" consisted of cases where a definite decrease in tumor size was recognized clinically, and included all those that failed to attain the "markedly effective" grade.

TABLE 1. Regression of Tumor size after Chemotherapy

Cases	Markedly Effective	Effective	Non-Effective
191	43 (22.5%)	88 (46.0%)	90 (31.4%)

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2) Results of single and combination therapy: In Tables 2 and 3 are shown the cases treated with different agents, namely, Nitromin, Actinomycin C, Mitomycin C, Endoxan, and others. A comparison of their therapeutic efficacies revealed that between these chemical agents no clear difference was obtained clinically, as judged by the grades of tumor regression, and other clinical signs, such as fall in body temperature, improvements in anemia, erythrocyte sedimentation rate or subjective symptoms. However, efficacy of therapy with steroid hormone (single therapy) was found to be superior to those with other chemotherapeutic agents.

Tables 4 and 5 show the results of combination therapy with two or more agents. Compared with the results of single therapy above described there was noted in general better efficacy, as evidenced by the grades of tumor regression and other clinical findings. When the effects on tumor regression are studied, it will be seen that in case of single therapy the results were, "markedly effective" 18.4%, "effective" 45.2% and "non-effective" 36.3%, while incase of combination therapy the results were, 35.5%, 48.8% and 15.5%, respectively (Table 6). Further, when steroid hormone was used in combination therapy, as may be seen from Table 4 and 5.

In the therapy of malignant lymphoma the finding that steroid hormone alone is highly effective in producing regression of tumor ("markedly effective" 23.3%, "effective" 63.3%) deserves attention (Table 6).

3) Selection of chemotherapeutic agents and lymphadenogram: In under-

TABLE 2. Tumor regression after Single therapy

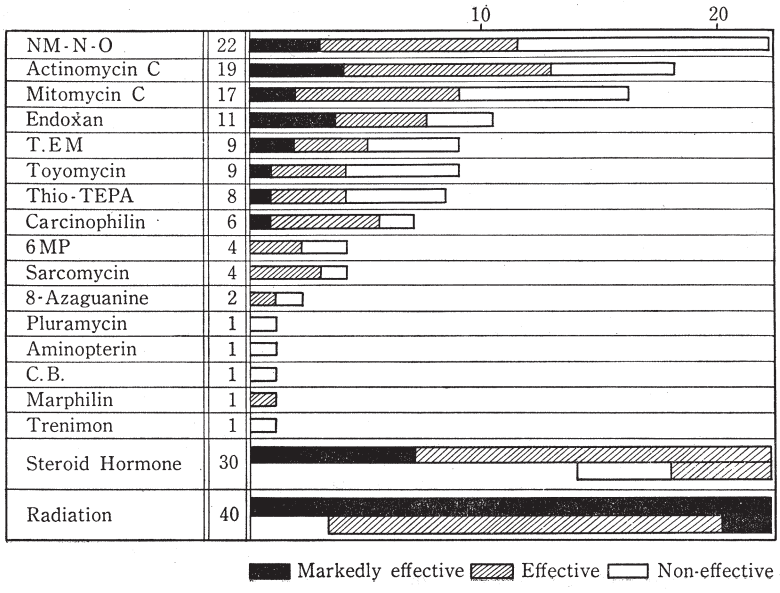


TABLE 3. Improvement in various clinical findings after single therapy

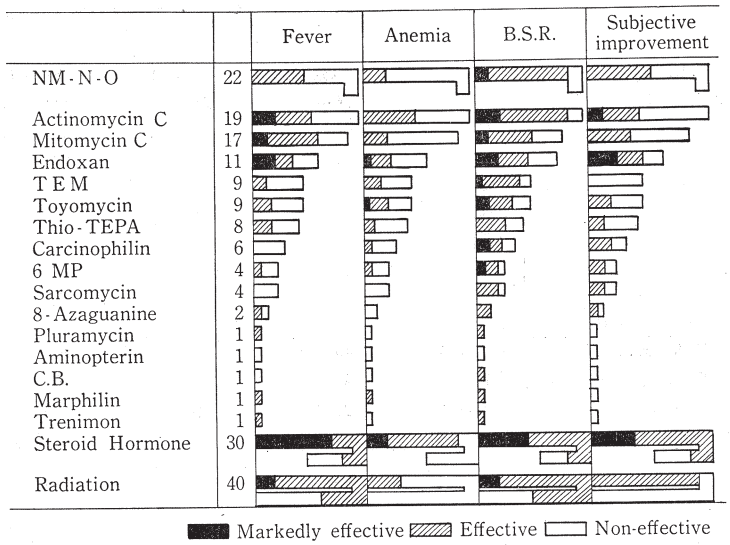
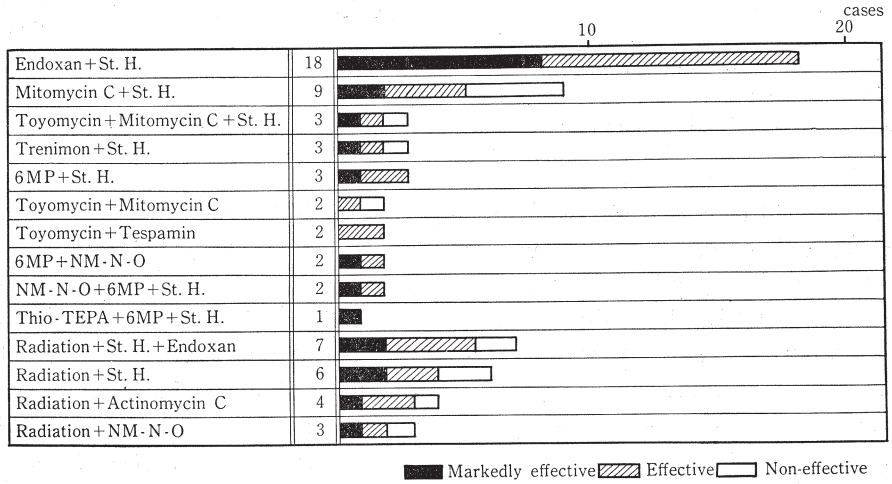


TABLE 4. Regression of Tumor size after combination therapy



taking chemotherapy it is very important to study what agent to administer and how, single or combined. Table 7 shows a "lymphadenogram" prepared by Dr. Ono. A lymphadenogram is constructed by observation of two thousand random cells on smears prepared by needle biospy material of the lymphoma, or stamp preparation of the excised lymphoma, and obtaining the percentages of mature lymphocytes, immature cells, reticulum cells and myeloid cells, by classification of the 2,000 cells into the above four main cell types. The bars of the table represent the lymphadenogram for each case. When reticulum

TABLE 5. Improvement in various clinical findings after combination therapy

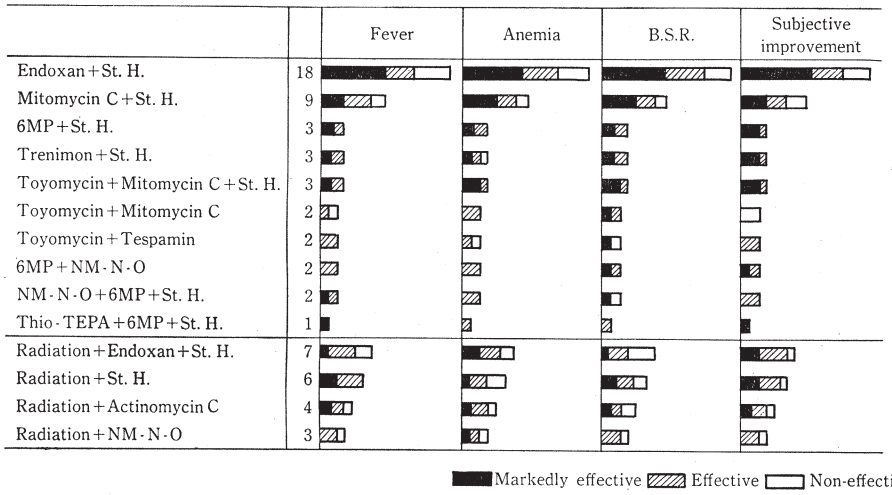


TABLE 6. Regression of Turmor size after single chemotherapy or combination chemotherapy

		Markedly effective	Effective	Non-effective
Cases of single chemotherapy	147	27 (18.4%)	66 (45.2%)	54 (36.3%)
St. H therapy	30	7 (23.3%)	19 (63.3%)	4 (13.3%)
Cases of combination chemotherapy	45	16 (35.5%)	22 (48.8%)	7 (15.5%)

cells, myeloid cells and mature lymphocytes are found intermixed and present a variegated pattern, the cases are mainly Hodgkin's Disease. When the lymphadenogram of a lymphoma assumes a pattern alike Hodgkin's Disease, steroid hormone should be the main therapeutic agent to be used, and in general, cases showing such a lymphadenogram respond well to therapy. However, when immature cells preponderate, namely, in cases of lymphoreticulosarcoma and lymphosarcoma, alkylating agents or other anti-cancer drugs have to be used. In these cases the combined use of steroid hormone is an advantage, but the efficacy of chemotherapy is relatively low.

On comparing the tumor regression effects of anti-cancer drugs on lymphoreticulosarcoma and lymphosarcoma with those on Hodgkin's Disease, "markedly effective" was 20% in the former and 31% in the latter, indicating a higher drug sensitivity in Hodgkin's Disease.

4) Tumor spread and efficacy of chemotherapy: In Table 8, (A) represents the case group with localized lymphoma, and (B) that with generalized spread accompanied by hepatomegaly and splenomegaly. When the tumor regression effects in these two groups were observed, the effective (including markedly

TABLE 7. Lymphadenogram

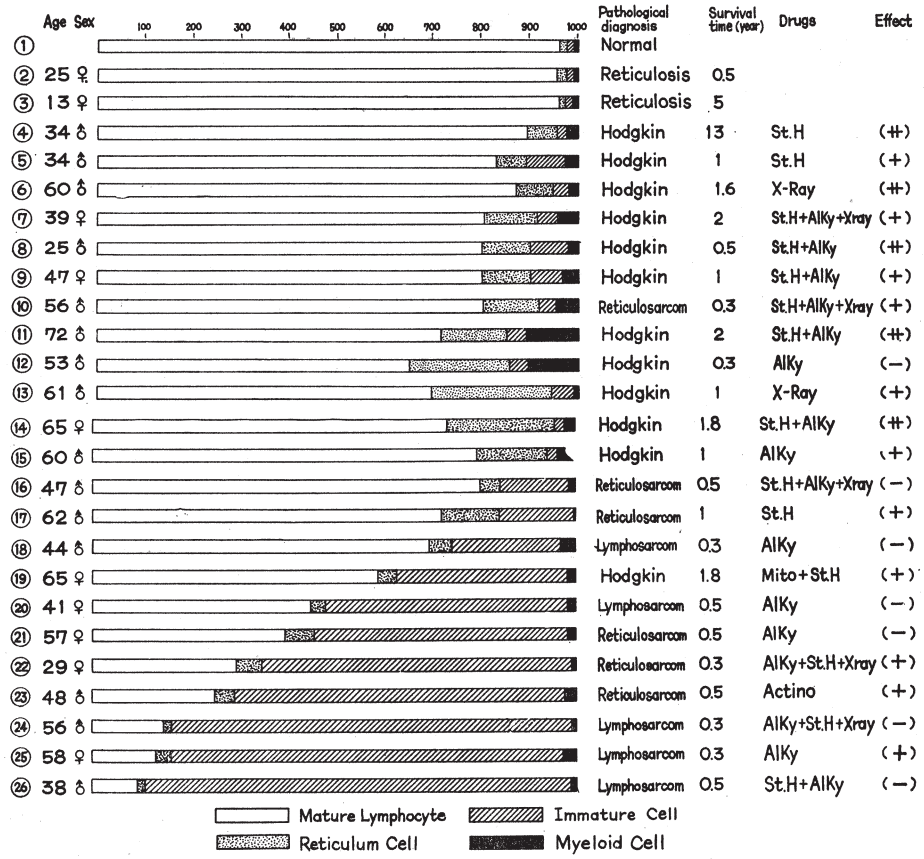


TABLE 8. Tumor spread and efficacy of chemotherapy

	A		B	
Cases	87		48	
	Effective	Non-effective	Effective	Non-effective
	55 63.2%	32 36.8%	22 45.8%	26 54.2%
Steroid Hormone	6	5	3	1
Anti-cancer drugs	11	14	1	8
Steroid Hormone+anti-cancer drugs	18	9	11	10
Radiation	8	1	0	0
Radiation+St. H.	3	0	1	1
Radiation+anti-cancer drugs	5	1	0	1
Radiation+anti-cancerdrugs+St. H.	4	2	6	5

A: Case group with localized lymphoma.
B: Case group with generalized spread and/or accompanied by hepatomegaly and splenomegaly.

effective) was 63.2% and the non-effective 36.8% in Group (A), while the respective rates in Group (B) were 45.8% and 54.2%, indicating clearly more effective cases in Group (A). From Table 8, it will be also seen that in single therapy with steroid hormone or anti-cancer drug the effective and non-effective were approximately equal in number, but in case of combination therapy (steroid hormone with anti-cancer drug) then umber of effective cases became far greater. Contrary to the above, in the Group (B) non-effective cases were numerous with single therapy by steroid hormone or anti-cancer drug, and only with combination therapy did the numbers of effective and non-effective cases equal each other. In other words, when cases belonging to Group (B) are to be treated, the poor therapeutic effects have to be borne in mind and the need of therapy with combinations of two or more drugs must not be forgotten.

5) Side-effects: In Table 9 are shown the states of occurrence of side-effects following the administration of doses of drugs above a definitely effective level (a level for each drug expected to influence the tumor), according to each drug. The combined administration of steroid hormone should to some extent inhibit the appearance of side-effects, but as shown in Table 9, even in combination therapy with steroid hormone, when the dose of anti-cancer agents exceeds a definite level side-effects must be considered to occur in various forms.

6) Rate and duration of remission: We found that chemotherapy of malignant lymphoma may produce definite regression, as well as marked im-

TABLE 9. Side effects according to each drugs

	Cases	General fatigue	Symptom of digestive system	Symptom of nerve system	Symptom of cutaneous system*	Hemorrhagic tendency	Leucopenia
NM-N-O	22	7	15	0	0	4	7
Thio-TEPA	8	1	7	0	0	0	1
TEM	9	2	6	0	0	1	2
Actinomycin C	19	6	8	0	0	4	3
Carcinophilin	6	1	1	0	1	0	0
Mitomycin C	17	8	3	1	1	6	8
Endoxan	11	3	3	2	4	3	6
Toyomycin	9	2	2	1	3	0	1
Steroid Hormone	30	5	5	4	0	0	0
Endoxan+Steroid H.	18	2	6	3	8	2	6
Mitomycin C+Steroid H.	9	4	2	3	1	4	5
Trenimon+Steroid H.	5	1	1	0	2	1	2
Radiation	40	32	23	5	38	3	27
Radiation+St. H.	6	3	1	1	2	0	3
Radiation+Endoxan+St.H.	7	2	2	2	2	1	4

* Including alopecia and phlebitis

TABLE 10. Duration of remission

	~2 month	~6 month	~1 years	~5 years	~10 years	10 years~
Hodgkins disease	1	5	2	1	1	1
Lymphoreticulo sarcoma and lymphosarcoma		7				

provement of the diseased state. Such improvement in the pathological states is termed a remission. Namely, a remission is a state when improvement of the diseased state warrants a return to near normal life. On observing the duration of the remission, it will be seen from Table 10 that a clear difference exists between Hodgkin's Disease and lymphoreticulosarcoma and/or lymphosarcoma, the duration of Hodgkin's Disease being definitely longer. In case of Brill-Symmer's Disease the duration of remission was in all cases over one years.

SUMMARY

In the chemotherapy of malignant lymphoma there are sometimes encountered cases that respond surprisingly well, as judged by the regression or loss of the tumor and improvement of the general condition. Despite this, prolongation of life of these cases by chemotherapy has not been fully attempted so far. The selection of the chemotherapy has not been fully attempted so far. The selection of the chemotherapeutic agents and the method of administration will depend on the type and extent of the tumor. When immature cells exist in high percentage in the tumor, combination therapy must be adopted, so that incases of lymphoreticuloarcoma and slymphosarcoma combination therapy becomes necessary. Again, when lymphoma are recognized throughout the entire body, chemotherapy has to be conducted vigorously. Rate and duration of remission were also found to be influenced largely by the nature of the tumor. The histologic and cytologic findings of these tumors as related to the efficacy of chemotherapy are believed to present material for consideration in the clinical aspects of various chemotherapeutic agents on these types of tumor, and it was realized that the findings can contribute to no small degree in the solution of various problems connected with the therapy of cancer. From such a standpoint we have been investigating the chemotherapy of malignant lymphoma, and by continuing to devise various means and ways to improve existing chemopeutic methods, we hope to raise the remission rates in malignant lymphomas and thereby prolong the life span of patients with this disease.

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REFERENCES

1) Gall, E. A. and Mallory, T. B., Malignant Lymphoma, *Amer. J. Path.*, **18**, 381, 1942.
2) Lumb, C., Tumors of Lymphoid Tissue. Baltimore, Williams and Wilkins., 1957.
3) Reinhard, E. H., Good, J. T. and Martin, E., Chemotherapy of Malignant Neoplastic Diseases, *J.A.M.A.*, **142**, 383, 1950.
4) Burchenal, J. H. and Oettgen, H. F., Chemotherapy. Cancer Progress, London, Butlerworth, 1960.
5) Heller, J. R., The role of Chemotherapy in Lymphomas. In Treatment of Cancer and Allied Diseases. New York, Harper and Row, 1964.