Acta Medica Okayama

Volume 42, *Issue* 5 1988 *Article* 6

OCTOBER 1988

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Abstract

We studied the correlation between the cell surface markers and prognosis of non-Hodgkin's lymphoma (NHL) patients treated in the Shikoku Cancer Center Hospital from 1980 to 1986. Thirty-one cases were selected on the basis of having a lymphnode as a primary lesion, having been immunophenotyped before chemotherapy, being in the intermediate histologic grade and being in stage II, III or IV. Thirteen cases of the T-cell type (T-lymphomas) and 18 cases of the B-cell type (B-lymphoma) were identified. The complete remission rate was 54% among T-lymphoma patients and 78% among B-lymphoma patients. The median length of survival was 12+ months in T-lymphoma and 26+ months in B-lymphoma. The survival rate of T-lymphoma patients was significantly lower than that of B-lymphoma patients. The importance of making surface marker studies was reappraised in our study.

KEYWORDS: surface marker, prognosis, non-Hodgkin's lymphoma, T-cell type, B-cell type

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*PMID: 3265575 [PubMed - indexed for MEDLINE]

Acta Med Okayama 42 (5) 287-292(1988)

Importance of Cell Surface Marker to the Prognosis of Non-Hodgkin's Lymphoma

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We studied the correlation between the cell surface markers and prognosis of non-Hodgkin's lymphoma (NHL) patients treated in the Shikoku Cancer Center Hospital from 1980 to 1986. Thirty-one cases were selected on the basis of having a lymphnode as a primary lesion, having been immunophenotyped before chemotherapy, being in the intermediate histologic grade and being in stage II, III or IV. Thirteen cases of the T-cell type (T-lymphomas) and 18 cases of the B-cell type (B-lymphoma) were identified. The complete remission rate was 54% among T-lymphoma patients and 78% among B-lymphoma patients. The median length of survival was 12+ months in T-lymphoma and 26+ months in B-lymphoma. The survival rate of T-lymphoma patients was significantly lower than that of B-lymphoma patients. The importance of making surface marker studies was reappraised in our study.

Key words : surface marker, prognosis, non-Hodgkin's lymphoma, T-cell type, B-cell type

Non-Hodgkin's lymphoma (NHL) is a malignancy, in which chemotherapy and radiotherapy effectively induce remission and prolong survival. Several risk factors for NHL, *e.g.,* high serum lactate dehydrogenase levels and bulky masses, have been defined by statistical study using multivariant analysis (1, 2). A few reports from the United States and European countries have reported the use of surface markers of lymphoma cells in determining the prognosis (3-5), but there is no mention of surface markers in the Working Formulation (6), which was established to classify the histologic subtypes in relation to prognosis.

NHL may be classified into two groups according to the surface marker, the T-cell type (T-lymphoma) and B-cell type (B-lymphoma). The prognosis of T-lymphomas has generally been reported poor in our country (7, 8).

We report herein our data concerning NHL, emphasizing the significant difference with regard to the prognosis between T-lymphoma patients and B-lymphoma patients. Approximately 40% of the B-lymphoma patients received adequate treatment by chemotherapy survived for a long time. T-lymphoma patients had a worse remission rate and a shorter time than B-lymphoma

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patients.

Materials and Methods

We analyzed the records of NHL patients treated in our hospital from July 1980 to December 1986, and selected 31 patients for the study of the correlation between surface markers and prognosis. The cases were all immunophenotyped before chemotherapy, classified histologically into the intermediate grade and defined as stage II, III or IV. All of the patients had lymphadenopathy, which was considered the primary lesion. The cases with primary lesions of Waldeyer's ring or extranodal organs were excluded.

The diagnosis of NHL depended upon the histological classification of the Lymphoma Study Group (LSG) of Japan (9). The histologic subtypes of the LSG classification can be translated into those of the classification of the Working Formulation (10). In this study, we excluded cases of follicular lymphoma, diffuse lymphoma of either the small-cell type or the pleomorphic type, lymphoblastic lymphoma and Burkitt's lymphoma. Two cases of adult T-cell leukemia (ATL) with typical leukemia symptoms also were not included.

The examination of surface markers of lymphoma cells was performed by standard immunological methods. Briefly, single cell suspension of a part of the biopsied lymph-node was prepared by passing the biopsied material through a stainless steel mesh. At the time, when monoclonal antibodies were not commercially available, rosette formation of sheep erythrocytes around the lymphoma cell was the criteria of the T-cell type. In order to define the B-cell type, the monoclonality of reactivity against a heavy and light chain of immunoglobulin, which was labeled with fluorescein isothiocyanate (FITC), was determined by a microscopic immunofluorescence method. After monoclonal antibodies became available, an indirect immunofluorescence method using purified antibodies and FITC-labeled anti-mouse sheep serum was employed to identify positive cells under the microscope. The main monoclonal antibodies for defining the T-cell marker were CD3(Leu-4), CD4(Leu-3a), CD8(Leu-2a) (Becton Dickinson Monoclonal Center, Mountain View, CA, USA), and CD11 (OKT-11) (Ortho Diagnostic System, Raritan, NJ, USA), and those for the B-cell marker were CD19 (B4) and CD20 (B1) (Coulter Immunology, Hialeah, FL, USA). A positive reaction against CD3 and CD11 with either CD4 or CD8 in conjunction with negative reactions against CD19 and CD20 and against the series of immunoglobulins was mainly considered to define T-lymphomas. B-lymphomas were defined by a positive reaction against CD19 or CD20 as well as positive reactions against one of the light chains and one or two heavy chains of immunoglobulins. B-lymphomas were not reactive against T-related monoclonal antibodies (11).

The staging procedures recommended by the Ann Arbor Conference (12) were performed. They included bone marrow examination, bipedal lymphangiography, computed tomography, abdominal ultrasound and gallium scintigraphy.

Four parameters (anti-human T-lymphotropic virus (HTLV)-I antibody, lymphoma cells in peripheral blood, lymphoma cells in bone marrow and bulky mass) were reviewed to characterize the clinical background of the patients. Anti-HTLV-I antibody was tested by the methods of indirect immunofluorescence using the MT-2 cell line (courtesy of Dr. I. Miyoshi, Kochi Medical College, Kochi, Japan) and enzyme-linked immunosorbent assay (ELISA) using a kit (Eisai Co., Ltd. Tokyo, Japan) (13). Smear prep-

arations of peripheral blood and bone marrow were stained with Wright-Giemsa and examined for lymphoma cells under a microscope. More than 0.4% lymphoma cells in the bone marrow, or more than 1% lymphoma cells in the peripheral blood were considered as positive findings of NHL.

The major and minor axes of a swollen lymphnode were measured, and bulky mass was defined as a mass with an axis of more than 5 cm.

All patients were treated with combination chemotherapy using the CHOP regimen (adriamycin, cyclophosphamide, vincristine and prednisolone) (14). After achieving a complete remission (CR), the same drug combination at a modified dose was given every 4 weeks for one year as a maintenance therapy (15). Patients, who did not achieve a CR, were given radiotherapy and other chemotherapy drugs, intensively, with sufficient supportive care.

The difference in the survival rate between T-lymphoma patients and B-lymphoma patients was statistically analyzed. Survival duration was defined as the period from the first day of chemotherapy to the date of death or the censored date (March 31, 1988). The minimal observation period was 15 months from the start of chemotherapy. A survival rate curve was drawn by Kaplan-Meier's method, and the generalized Wilcoxon method was used to examine differences between the two groups.

Results

Patient characteristics with regard to the stage of disease, anti-HTLV-I antibody, lymphoma cells in peripheral blood, lymphoma cells in bone marrow and bulky mass are shown in Table 1. The histologic subtypes of T-lymphomas were 1 diffuse, medium-cell type; 6 diffuse, mixed type and 6 diffuse, large-cell type. B-lymphomas included 6 diffuse, medium-cell type; 1 diffuse, mixed type, and 6 diffuse, large-cell

Table 1 Patient characteristics

	Number of patients		χ^2-test
	T-lymphomas	B-lymphomas	
Total number	13	18	
Stage			
II	2	3	
III	7	8	N.S.[a]
IV	4	7	
Anti-HTLV-I antibody			
Negative	8	16	
Positive	3	2	N.S.
Not examined	2	0	
Lymphoma cells in peripheral blood			
No	11	18	N.S.
Yes	2	1	
Lymphoma cells in bone marrow			
No	9	14	N.S.
Yes	4	4	
Bulky mass			
No	9	13	N.S.
Yes	4	5	

a: N.S.: no significance ($p > 0.05$) by chi-square test.

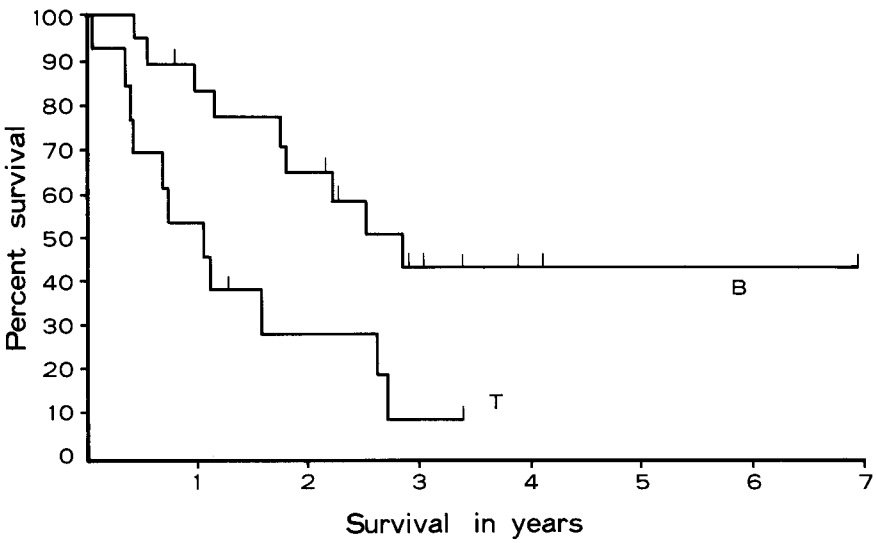

Fig. 1 Kaplan-Meier plots of survival curves of T-lymphoma (T) and B-lymphoma patients (B). The survival rates between T ($n=13$) and B ($n=18$) were significantly different ($p < 0.05$) according to the generalized Wilcoxon test.

type. No significant deviations were observed between T-lymphomas and B-lymphomas as background factors, according to chi-square examination.

The complete remission rate of T-lymphomas and B-lymphomas was 54% and 78%, respectively. The median survival period was 12+months in T-lymphomas and 26+months in B-lymphomas.

To assess the difference in the prognosis of the patients, the survival rate curves of both groups were drawn by Kaplan-Meier's method (Fig. 1). This assessment indicated a poor prognosis for T-lymphomas. The B-lymphoma curve became flat after 3 years from the start of chemotherapy. The difference in the survival rate between T-lymphomas and B-lymphomas was significant ($p < 0.05$) according to the generalized Wilcoxon test.

Discussion

Our data confirmed the poor prognosis of T-lymphoma patients, who have a low CR rate and short survival time, compared with B-lymphoma patients. As there is a difference in disease behavior between T- and B-lymphomas, probably due to the different origin of the malignant cells, it is necessary to divide the clinical entity of NHL into two types (T-lymphoma and B-lymphoma types) when the results of therapy and the prognosis of patients on chemotherapy are discussed.

In the United States and European countries, the percentage of T-lymphomas is so low (16) that the existence of T-lymphomas among all NHL cases is ignored in clinical data. Interesting, but contradictory, data have been reported by Cossman *et al.* in the United States (5). Their date showed 42% T-lymphomas and 53% B-lymphomas out of 57 patients who had been immunophenotyped before therapy. The length of survival was reported as not being significantly different between the two groups.

The Lymphoma Study Group(1978-1980) in Japan reported the chemotherapy results of 100 NHL patients (8). Their study included all histologic subtypes. Their results

showed that the prognosis of T-cell lineage lymphoma patients was worse than that of B-cell type patients, although there existed a bias of a large majority of T-cell type patients because it was a nationwide study. In order to exclude the bias of histologic subtypes, we studied the correlation between surface markers and prognosis in patients with an intermediate-grade histology.

In our country, the frequency of T-lymphomas and B-lymphomas varies from place to place (17). For this reason, the overall outcome of therapy for NHL may be worse in a district where T-lymphomas are prevailing than in a district where T-lymphomas are scarcely found.

The reason for the low CR rate and poor prognosis of T-lymphomas is unclear. The biological properties of T-lymphoma cells regarding chemosensitivity and early drug resistance might provide a reason. Most T-lymphoma patients in incomplete remission died within 3 years due to tumor progression complicated with opportunistic infection. A few exceptional cases with low tumor burden, however, have survived for long periods as a result of chemotherapy and radiotherapy. To determine the risk factors for T-lymphomas, statiatical analysis using multivariant analysis needs to be employed in further studies.

About 40% of B-lymphoma patients are anticipated to survive a considerable length of time, and we can use the term "cure" for such cases in our hospital, because there are very few patients who die after 3 years' observation. In contrast, 60% of the patients die within 3 years, even though they were in complete remission initially. When the tumor relapsed, these patients were treated intensively with other drugs including newly-developed drugs. The survival of relapsed patients was poor. A new strategy of treatment to improve the survival rate of these patients needs to be explored.

In conclusion, the cell surface marker is an important factor influencing the prognosis of NHL. The prognosis of T-lymphomas is worse than that of B-lymphomas in our district.

Acknowledgments. The authors thank Dr. Shosuke Moriwaki for expert review of pathological specimens and staff doctors for helping us with the patients' care at Shikoku Cancer Center Hospital.

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare of Japan (No. 61-2).

References

1. Cabanillas F, Burke JS, Smith TL, Moon TE, Butler JJ and Rodriquez V: Factors predicting for response and survival in adults with advanced non-Hodgkin's lymphoma. Arch Intern Med (1978) **138**, 413-418.
2. Fisher RI, Hubbard SM, DeVita VT, Berard CW, Wesley R, Cossman J and Young RC: Factors predicting long-term survival in diffuse mixed, histiocytic, or undifferentiated lymphoma. Blood (1981) **58**, 45-51.
3. Bloomfield CD, Kazimiera JG, Frizzera G, Kersey JH and Goldman AI: Clinical utility of lymphocyte surface markers combined with the Lukes-Collins histologic classification in adult lymphoma. N Engl J Med (1979) **301**, 512-518.
4. Rudders RA, Delellis .RA, Ahl ET, Bernstein S and Begg CB: Adult non-Hodgkin's lymphoma. Correlation of cell surface marker phenotype with prognosis, the new Working Formulation, and the Rappaport and Lukes-Collins histomorphologic schemes. Cancer (1983) **52**, 2289-2299.
5. Cossman J, Jaffe ES and Fisher RI: Immunologic phenotypes of aggresive, non-Hodgkin's lymphomas. Correlation with clinical features. Cancer (1984) **54**, 1310-1317.
6. The Non-Hodgkin's Lymphoma Pathologic Classification Project : National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and descripiton of a Working Formulation for clinical usage. Cancer (1982) **49**, 2112-2135.
7. Kimura I, Ohnoshi T, Tsubota T, Hiraki S and Hayashi K: Surface marker study of non-Hodgkin's lymphoma. Correlation with therapy with special reference to chemotherapy. Jpn J Cancer Clin (1980) **26**, 1160-1168 (in Japanese).
8. Lymphoma Study Group (1978-1980): Final results of cooperative study of VEPA [vincristine, cyclophosphamide (Endoxan), prednisolone and adriamycin]

therapy in advanced adult non-Hodgkin's lymphoma. Relation between T- or B-cell phenotype and response. Jpn J Clin Oncol (1982) **12**, 227-238.
9. Suchi T, Tajima K, Nanba K, Wakasa H, Mikata A, Kikuchi M, Mori S, Watanabe S, Mohri N, Shamoto M, Harigaya K, Itagaki T, Matsuda M, Kirino Y, Takagi K and Fukunaga S: Some problems on the histopathological diagnosis of non-Hodgkin's malignant lymphoma, a proposal of a new type. Acta Pathol Jpn (1979) **29**, 755-776.
10. Nanba K and Sasaki N: Histopathological classification of non-Hodgkin's lymphoma. Comparison between the new Working Formulation and Japanese LSG classification. Naika (1981) **48**, 14-20 (in Japanese).
11. Shimoyama M: Monoclonal antibodies and immunodiagnosis of leukemia/lymphoma. Acta Haematol Jpn (1985) **48**, 1711-1730.
12. Carbone PP, Kaplan HS, Musshoff K, Smithers DW and Tubiana M: Report of the committee on Hodgkin's disease staging classification. Cancer Res (1971) **31**, 1860-1861.
13. Taguchi H, Sawada T, Fujishita M, Morimoto T, Niiya K and Miyoshi I: Enzyme-linked immunosorbent assay of antibodies to adult T-cell leukemia-associated antigens. Jpn J Cancer Res (Gann) (1983) **74**, 185-187.
14. McKelvey EM, Gottlieb JA, Wilson HE, Haut A, Tally RW, Stephens R, Lane M, Gamble JF, Jones SE, Grozea PN, Gutterman J, Coltman C and Moon TE: Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer (1976) **38**, 1484-1493.
15. Toki H, Okabe K, Ishikawa M, Fujii M and Kimura Y: Remission maintenance therapy of non-Hodgkin's lymphoma by CHOP protocol. Jpn J Cancer Chemother (1984) **11**, 260-264 (in Japanese).
16. Kadin ME, Berard CW, Nanba K and Wakasa H: Lymphoproliferative diseases in Japan and western countries. Hum Pathol (1983) **44**, 745-772.
17. The T- and B-cell Malignancy Study Group: Stastical analyses of clinico-pathological, virological and epidemiological data on lymphoid malignancies with special reference to adult T-cell leukemia/lymphoma. A report of the second nationwide study of Japan. Jpn J Clin Oncol (1985) **15**, 517-535.

Received January 28, 1988; revised May 2, 1988; accepted July 5, 1988