Jpn. J. Cancer Res. 80, 720–726, August 1989

T-Cell Phenotype Is Associated with Decreased Survival in Non-Hodgkin's Lymphoma

Kazuyuki Shimizu,[1] Nobuyuki Hamajima,[2] Kazunori Ohnishi,[3] Kazuo Hara[4] and Akira Kunii[5]

[1]Department of Medicine, Fujita Gakuen Health University School of Medicine, Kutsukake-cho, Toyoake, Aichi 470-11, [2]Department of Preventive Medicine and [3]First Department of Internal Medicine, Nagoya University School of Medicine, Tsuruma-cho 65, Showa-ku, Nagoya 466, [4]Department of Pathology, Aichi Medical College, Nagakute-cho, Aichi 480-11 and [5]Department of Medical Technology, Nagoya University, Daiko-cho, Higashi-ku, Nagoya 461

This study was undertaken to determine which if any pretreatment factors are statistically significant determinants of the clinical outcome in patients with non-Hodgkin's lymphoma. The pretreatment factors in 20 patients with T-cell lymphoma, including two patients with adult T-cell leukemia/lymphoma (ATLL), and 28 patients with B-cell lymphoma were evaluated. In a stepwise logistic regression analysis, a T-cell phenotype in addition to high grade histology and pleural involvement demonstrated a statistically significant correlation with decreased response rate, when the analysis did not include patients with ATLL. Analysis by means of the Cox proportional hazards model disclosed that the T-cell phenotype retained a statistically significant correlation with survival after adjustments for other prognostic factors, whether the study included the patients with ATLL or not. The decreased response rate and survival of Japanese patients with non-Hodgkin's lymphoma in comparison with those reported in Western countries seem to be due to increased intrusion of T-cell lymphomas. To permit a reliable comparison of reports on new chemotherapeutic regimens from different institutions, the tumor phenotype must be determined in the population studied.

Key words: Non-Hodgkin's lymphoma — T-cell phenotype — Prognostic factors — Multivariate analyses

Follicular lymphoma in Japan accounts for less than 10% of all non-Hodgkin's lymphomas (NHL), in contrast to the 30–35% seen in Western countries, and diffuse lymphoma of low grade malignancy is also uncommon.[1,2] To minimize the influence of uneven distributions in tumor histology between different institutions, recent studies which compare the efficacy of new chemotherapeutic regimens in the treatment of NHL have been performed predominantly on patients with diffuse lymphoma of intermediate and high grade malignancy.[3–6] However, because diffuse lymphomas contain both B- and T-cell lymphomas, whose clinical behavior is different,[7–10] the problem of immunophenotypes still remains. The incidence of NHL in Japan with a T-cell phenotype has been reported to be as high as 75% in endemic and 40% in nonendemic areas, whereas it is only 10–20% in Western countries.[1,2] Overall, the histologic and immunologic distribution of Japanese NHL is believed to contribute unfavorably to the prognosis.[11] Thus, the excellent results achieved in recent studies of patients with diffuse large cell lymphoma treated with second or third generation chemotherapies in Western countries[3,4] cannot be expected in Japanese patients with the same histology because of the intrusion of T-cell lymphoma.

However, because the number of patients with NHL in Japan is not as great as in Western countries, and also because the number of patients with T-cell lymphoma is limited in the West, few studies have attempted to correlate immunologic features with the clinical presentation and response to therapy in Japan or in Western countries.

We have treated patients with stage III or IV NHL of intermediate and high grade malignancy with a new chemotherapeutic regimen composed of first generation agents, but administered under third generation therapeutic protocols.[6] In the present report, we have attempted to establish the predictive value of pretreatment factors in the response rate and survival by correlating the immunophenotypes with clinicopathologic features.

MATERIALS AND METHODS

Study group Between January 1981 and September 1986, 87 previously untreated patients were diagnosed, worked-up and treated for NHL at the First Department of Internal Medicine, Nagoya University Hospital, in Nagoya. Among the 87 patients, 20 patients with ad-

[1] To whom communications should be addressed.

vanced T-cell lymphoma and 28 patients with advanced B-cell lymphoma of intermediate or high grade malignancy were admitted into this study. The remaining 39 patients were not included, because of localized disease and/or favorable histology. The initial treatments employed in these 39 patients were radiation and/or mild chemotherapy such as COP (cyclophosphamide, vincristine and prednisolone) or VEMP (vincristine, cyclophosphamide, 6-mercaptopurine and prednisolone). The current analysis was performed in February 1989. Follow-up time was calculated from the initiation of chemotherapy, with a mean follow-up of 29 months and a range of 3 to 94 months.

Patients were staged according to the Ann Arbor classification.[12] Pretreatment staging studies included complete blood counts, routine liver function tests, chest radiograph, lymphangiogram, computed tomographic (CT) scans of the chest and abdomen, ^{99m}Tc sulfur colloid liver and spleen scan, ^{67}Ga scan and bone marrow examination. In some patients, biopsy of the skin, stomach and/or the liver, or thoracocentesis was done.

Histologic diagnosis was made according to the Lymphoma Study Group (LSG) classification of Japan,[13] and the histology grading was determined according to the working formulation for clinical usage.[14]

Immunophenotypic studies Lymphoma cells obtained from a lymph node or extranodal tumor biopsy specimen were subjected to surface marker studies. Identification of the T-cell phenotype was performed by a sheep erythrocyte rosetting (E-rosette) technique early in the study and by an indirect immunofluorescence technique using different monoclonal antibodies subsequently. Identification of the B-cell phenotype was performed by a direct immunofluorescence technique using FITC-conjugated rabbit anti-human immunoglobulin or/and by an indirect immunofluorescence technique using monoclonal antibodies. The monoclonal antibodies used were Leu-1, 2a, 3a, 4, 7 and HLA-DR, Becton-Dickinson, Mountain View, CA; B1, Coulter, Hialeah, FL; and OKT 3, 4, 6, 8, 9 and 10, Ortho Pharmaceutical Corp., Raritan, NJ. In some patients, immunophenotypes were identified by immunohistochemical studies performed on unfixed frozen cryostat sections of an excised lymph node or specimen of extranodal tumor, as described previously.[15]

Treatment Remission induction chemotherapy was "weekly CHOP"[6] (cyclophosphamide 450 mg/m^2, doxorubicin 20 mg/m^2 and vincristine 1 mg every week) until all measurable tumors disappeared. Oral prednisolone 30 mg/day was given during the initial week of therapy with subsequent tapering to a maintenance dose of 5 mg/day.

Those patients who achieved a complete remission received a maintenance chemotherapy for 2 years consisting of daily oral cyclophosphamide 50 mg, 6-mercaptopurine 50 mg, and prednisolone 5 mg, and biweekly intravenous injections of vincristine 1 mg (VEMP).

Definition of response Patients who appeared to have a complete remission (CR) clinically were evaluated for the presence of residual tumor by repeating any previously abnormal staging studies, including appropriate biopsies. Patients who were considered to be free of disease after restaging, were defined as being in CR. Patients who failed to achieve a clinical CR but showed greater than a 50% reduction in clinically measurable tumor for at least one month were defined as being in partial remission (PR). No response (NR) included patients with progressive disease, only temporary regression, or early death.

Screening for human T-cell leukemia virus type I (HTLV-I) Sera from patients with T-cell lymphoma were sent to the Special Reference Laboratory, Tokyo, to be examined for antibodies to HTLV-I by enzyme-linked immunosorbent assay (ELISA) or the gelatin particle agglutination (PA) method to confirm the diagnosis of adult T-cell leukemia/lymphoma (ATLL).[16]

Prognostic factors The factors evaluated for potential prognostic significance are outlined in Tables I and II and included sex, age, clinical stage, symptom status, site of involvement, number of extranodal sites, serum lactic dehydrogenase (LDH) level, serum alkaline phosphatase (ALP) level, performance status (PS), histology grading according to the working formulation,[14] hemoglobin level, total protein level, and immunophenotype.

Statistical methods Multiple statistical analyses were performed at the Department of Preventive Medicine, Nagoya University School of Medicine. Univariate analyses of the unadjusted association of each prognostic factor with immunophenotype were conducted using Fisher's test for 2×2 contingency tables.[17] A logistic regression analysis[17] was performed to identify the important factors influencing the response according to the LOGIST procedure[18] of the Statistical Analysis System (SAS) program[19] (SAS Institute, Cary, NC).

Survival was calculated from the date of initiation of treatment until the last follow-up date or death. Survival curves were constructed according to the Kaplan-Meier method.[20] Multivariate analysis using the Cox proportional hazards model[21] according to the PHGLM procedure[22] of the SAS program[19] was performed to identify the important factors influencing survival.

RESULTS

Correlation of prognostic factors with immunophenotypes Table I shows the distribution of patients with T- and B-cell lymphoma accodring to the various prognostic factors. Patients with T-cell lymphoma presented with more advanced disease statistically ($P<0.005$) and with

Table I. Pretreatment Patient Characteristics

Characteristic	T-cell phenotype (n=20)	B-cell phenotype (n=28)	P value[a]
Age			
≤65 years	15	24	
>65 years	5	4	NS[g]
Performance status			
0, 1	15	22	
2–4	5	6	NS
Clinical stage			
III	2	14	
IV	18	14	0.005
Symptom status[b]			
A	7	17	
B	13	11	NS
Site of involvement[c]			
Liver	13	8	0.05
Bone marrow and/or peripheral blood	8	7	NS
Pleura	4	3	NS
Skin	3	2	NS
Sinonasal cavity	3	0	NS
Thyroid	0	2	NS
GI tract	0	2	NS
Bone	0	2	NS
Number of extranodal sites			
0–1	12	24	
>2	8	4	NS
Histologic subtype (LSG)[d]			
Diffuse			
small	1	0	
medium	4	4	
mixed	4	2	
large	4	21	
pleomorphic	1	0	
others	1	0	
IBL-like T-cell[e]	5		
Histologic grade (WF)[f]			
Intermediate	14	23	
High	6	5	NS
LDH			
≤2.5×normal	10	16	
>2.5×normal	10	12	NS
ALP			
Normal	10	24	
Increased	10	4	0.05
Hemoglobin			
≥10 g/dl	18	27	
<10 g/dl	2	1	NS
Total protein			
≥6 g/dl	17	24	
<6 g/dl	3	4	NS

a) Fisher's exact test.
b) A and B denote the subcategory of each stage. The B classification will be given to those with (1) unexpected weight loss of more than 10% of the body weight in the 6 months before admission, (2) unexpected fever with temperature above 38°C, and/or (3) night sweats. The A classification will be given to those without these 3 constitutional symptoms.
c) Number of cases without involvement were omitted.
d) LSG, Lymphoma Study Group classification.
e) IBL-like T-cell, immunoblastic lymphadenopathy-like T-cell lymphoma.
f) WF, working formulation for clinical usage.
g) NS, not significant.

a significantly higher incidence of liver metastasis ($P<0.05$) than patients with B-cell lymphoma. The number of patients with increased serum ALP level was significantly lower with B-cell phenotype ($P<0.05$). Statistical analysis of the association between histologic subtypes (LSG classification)[13] and immunophenotype was not done because most diffuse large cell lymphomas occurred in patients with B-cell phenotype.

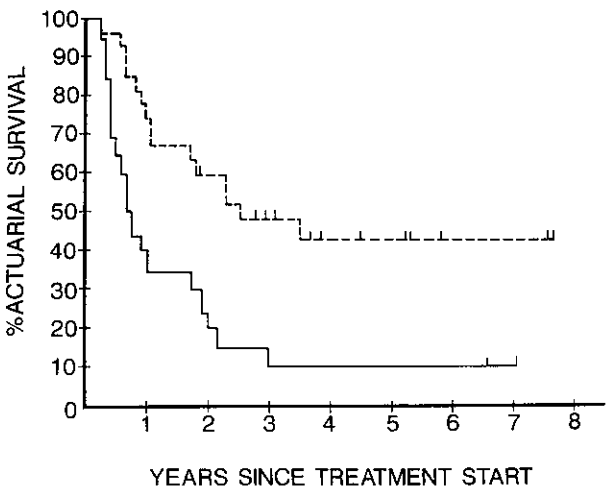

Fig. 1. Survival curves for patients with non-Hodgkin's lymphoma according to immunophenotypes. Slashes indicate patients alive and censored including one patient who died in autopsy-proven CR of gastric cancer. T-cell phenotype (——), B-cell phenotype (---).

Prognostic factors for CR in response to "weekly CHOP" Fifteen clinical factors determined at the time of diagnosis were evaluated individually for their relationship to response with the use of a logistic regression analysis. When all 48 patients were analyzed, only the high grade histology demonstrated a statistically significant ($P=0.02$) correlation with decreased response rate. Among the 20 patients with T-cell lymphoma, two were seropositive for HTLV-I and were identified as having ATLL. When these 2 patients with ATLL were excluded from the univariate analysis, age became statistically significant ($P=0.04$) in addition to the high grade histology. These factors were further examined in a stepwise logistic regression analysis to select those with the greatest influence on the response. When all 48 patients were analyzed, the high grade histology ($P=0.006$) and the presence of pleural involvement ($P=0.02$) were statistically significant. When the 2 patients with ATLL were excluded from the multivariate analysis, T-cell phenotype became statistically significant ($P<0.05$) in addition to the histology grading and pleural involvement.

Prognostic factors for survival Of the 20 patients with T-cell lymphoma, 7 achieved a CR, but 5 relapsed, leav-

Table II. Cox Proportional Hazards Model Analysis of Survival

Prognostic factor	Comparable group	Univariate *P* value		Multivariate (48 cases)		Multivariate (46 cases)[a]	
		(48 cases)	(46 cases)	*P* value	Beta	*P* value	Beta
Cell phenotype	(T/B)	0.0006	0.0005	0.0006	1.3007	0.0007	1.3491
Age	(≤65/>65)	0.4420	0.4456				
Sex	(M/F)	0.8809	0.8557				
Performance status	(0–1/2–4)	0.1036	0.0925				
Clinical stage	(III/IV)	0.0055	0.0055				
Symptom status	(A/B)	0.0072	0.0080				
Extranodal site	(0–1/≥2)	0.0431	0.0347				
Liver inv[b]	(−/+)	0.0043	0.0046				
Bone marrow inv[b]	(−/+)	0.2545	0.2282				
Pleural inv[b]	(−/+)	0.0004	0.0006	0.0000	2.1302	0.0001	2.0648
Histologic grade	(IG/HG)[c]	0.0049	0.0082	0.0052	1.1952	0.0103	1.1016
LDH	(N/H)[d]	0.0657	0.0702				
ALP	(N/H)	0.0239	0.0270				
Hemoglobin	(≥10/<10)	0.3273	0.2425				
Total protein	(≥6/<6)	0.2829	0.2772				

a) Two patients with ATLL were excluded.
b) inv, involvement.
c) IG/HG, intermediate grade/high grade.
d) N/H, normal/high.

Table III. Hazard Ratio of T-Cell Phenotype as Opposed to B-Cell Phenotype Adjusted for Other Prognostic Factors

Model	Beta	Hazard ratio	*P* value
All cases			
Cell phenotype (P)	1.2666	3.55	0.0006
P+clinical stage (CS)	1.0256	2.79	0.0071
P+CS+symptom status (SS)	1.0976	3.00	0.0043
P+CS+SS+high LDH (L)	1.1042	3.02	0.0044
P+CS+SS+L+histologic grade (HG)	1.0019	2.72	0.0096
P+CS+SS+L+HG+performance status (PS)	1.1026	3.01	0.0062
P+CS+SS+L+HG+PS+hemoglobin (HB)	1.1153	3.05	0.0067
P+all the other prognostic factors	1.4335	4.19	0.0043
ATLL excluded			
P+all the other prognostic factors	1.7022	5.49	0.0039

ing only 2 patients alive and censored. Of the 28 patients with B-cell lymphoma, 19 achieved a CR, but 5 relapsed, leaving 14 patients censored, including one patient who died in autopsy-proven CR of gastric cancer. Figure 1 shows the survival curves for patients with B- and T-cell lymphoma. The estimated 5-year survival for patients with T-cell lymphoma was 10%, with a median survival of 9 months, and was 44% for patients with B-cell lymphoma, with a median survival of 31 months.

The 15 clinical factors evaluated for predictive value for response were evaluated individually for their relationship to survival. Statistically significant ($P<0.05$) factors associated with survival by univariate analysis were: T-cell phenotype, clinical stage, symptom status, more than 2 extranodal involvements, liver involvement, pleural involvement, high grade histology, and increased ALP level, regardless of whether the analysis included the 2 patients with ATLL or not (Table II).

These factors were further examined to select those with the greatest influence on survival using a Cox proportional hazards model. The same three prognostic factors that retained their significance in a stepwise logistic regression analysis were also significant, regardless of whether the study included patients with ATLL or not, i.e., pleural involvement, T-cell phenotype, and high grade histology (Table II).

Effects of immunophenotype on survival were evaluated after sequential adjustment of each prognostic factor using the Cox proportional hazards model. As shown in Table III, T-cell phenotype retained its statistical significance after adjustments of other prognostic factors, regardless of whether the analysis included patients with ATLL or not. The estimated hazard ratio for the cell phenotype was four to five, indicating that the T-cell phenotype affected survival substantially.

DISCUSSION

With the advent of new chemotherapeutic regimens, the response rate and survival of patients with NHL in Western countries has improved greatly.[4] However, although the same chemotherapeutic regimens have been employed in the treatment of Japanese patients with NHL, results have been much less satisfactory.[11] The reason for this is believed to be an intrusion of T-cell lymphoma with an incidence of 40 to 75%, though concrete multivariate statistical analyses are lacking.

The multivariate analysis in the present study, using the Cox proportional hazards model, disclosed that the T-cell phenotype retained a statistically significant correlation with survival after adjustments for other prognostic factors, whether the study included the 2 patients with ATLL or not. ATLL, which has a strong geographical predilection for southwestern Japan, the island of Kyushu, is seen less frequently in other parts of Japan.[2] In the present study, 2 out of 20 patients (10%) with T-cell lymphoma, who had been born and had grown up in Kyushu, were seropositive to HTLV-I, and presented with clinicopathologic features compatible with ATLL. The inclusion of ATLL patients among T-cell lymphoma patients in a major university hospital in a large city, whether in an endemic area or not, is not overlooked in Japan, because people from Kyushu seeking jobs frequently emigrate to mainland Japan.

Some reports have claimed that the prognosis of patients with advanced peripheral T-cell lymphoma other than HTLV-I positive ATLL was comparable to that of advanced diffuse B-cell lymphoma,[23-25] but others disagreed.[9,26] However, the present study demonstrated that the T-cell phenotype still retains an important influ-

ence on survival even after excluding the 2 patients with ATLL from analysis. As shown in Fig. 1, the actuarial survival of patients with B-cell lymphoma reaches a plateau of 44%, with no death occurring beyond 43 months (survival plateau). This is comparable to the results achieved in Western patients with NHL treated by second generation chemotherapies. Thus, the poor prognosis of Japanese patients with NHL can be explained by the intrusion of T-cell lymphoma, whether HTLV-I positive or not.

The reason for the significantly poor prognosis of patients with T-cell lymphoma in the present study might be explained by the significantly lower CR rate in response to "weekly CHOP" of T-cell lymphoma (35%) than for B-cell lymphoma (68%) ($P<0.05$). In this regard, intensive modern chemotherapy may reduce the importance of T-cell phenotype as a prognostic factor by obtaining a large number of CRs. However, there are still some who doubt the efficacy of recent intensive chemotherapy in sustaining a long-term remission of T-cell lymphoma due to the severity of the disease as well as the high relapse rate.[26]

The efficacy of new chemotherapeutic regimens has been tested on patients with advanced NHL of diffuse large cell type.[3–5] However, as diffuse large cell lymphomas contain both B- and T-cell lymphomas, and the T-cell phenotype is an important prognostic factor influencing survival, future studies should be performed on patients with diffuse lymphoma whose immunophenotypes have been determined.

(Received March 22, 1989/Accepted June 9, 1989)

REFERENCES

1) Watanabe, S., Nakajima, T., Shimosato, Y., Shimoyama, M. and Minato, K. T cell malignancies: subclassification and interrelationship. *Jpn. J. Clin. Oncol.*, **9** (Suppl), 423–442 (1979).
2) Kadin, M. E., Berard, C. W., Nanba, K. and Wakasa, H. Lymphoproliferative diseases in Japan and Western countries: Proceedings of the United States-Japan seminar, September 6 and 7, 1982, in Seattle, Washington. *Hum. Pathol.*, **14**, 745–772 (1983).
3) Fisher, R. I., DeVita, V. T., Hubbard, S. M., Longo, D. L., Wesley, R., Chabner, B. A. and Young, R. C. Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. *Ann. Intern. Med.*, **98**, 304–309 (1983).
4) Klimo, P. and Connors, J. M. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. *Ann. Intern. Med.*, **102**, 596–602 (1985).
5) Coleman, M. Chemotherapy for large-cell lymphoma: optimism and caution. *Ann. Intern. Med.*, **103**, 140–142 (1985).
6) Shimizu, K., Hara, K. and Kunii, A. Weekly CHOP for the treatment of advanced intermediate and high grade non-Hodgkin's lymphoma. *Am. J. Clin. Oncol.*, **12**, 195–200 (1989).
7) Levine, A. M., Taylor, C. R., Schneider, D. R., Koehler, S. C., Forman, S. T., Lichtenstein, A., Lukes, R. J. and Feinstein, D. I. Immunoblastic sarcoma of T-cell versus B-cell origin: I. Clinical features. *Blood*, **58**, 52–61 (1981).
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.*, **12**, 227–238 (1982).
9) Greer, J. P., York, J. C. and Cousar, J. B. Peripheral T-cell lymphoma: a clinicopathologic study of 42 cases. *J. Clin. Oncol.*, **2**, 788–798 (1984).
10) Grogan, T. M., Fielder, K., Rangel, C., Jolley, C. J., Wirt, D. P., Hicks, M. J., Miller, T. P., Brooks, R., Greenberg, B. and Jones, S. Peripheral T-cell lymphoma: aggressive disease with heterogeneous immunotypes. *Am. J. Clin. Pathol.*, **83**, 279–288 (1985).
11) Shimoyama, M., Ota, K., Kikuchi, M., Yunoki, K., Konda, S., Takatsuki, K., Ichimaru, M., Ogawa, M., Kimura, I., Tominaga, S., Tsugane, S., Taguchi, H., Minato, K., Takenaka, T., Tobinai, K., Kurita, S., Oyama, A., Hisano, S., Kozuru, M., Matsumoto, M., Nomura, K., Takiguchi, T., Sugai, S., Yamaguchi, K., Hattori, T., Kinoshita, K., Tajima, K. and Suemasu, K. Chemotherapeutic results and prognostic factors of patients with advanced non-Hodgkin's lymphoma treated with VEPA or VEPA-M. *J. Clin. Oncol.*, **6**, 128–141 (1988).
12) Carbone, P. P., Kaplan, H. S., Musshoff, K., Smithers, D. W. and Tubiana, M. Report of the committee on Hodgkin's disease staging classification. *Cancer Res.*, **31**, 1860–1861 (1971).
13) 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.*, **29**, 755–776 (1979).
14) Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer*, **49**, 2112–2135 (1982).
15) Shimizu, K., Hara, K. and Kunii, A. Non-Hodgkin's lymphoma following Hodgkin's disease. A case report and

immunohistochemical corroboration. *Am. J. Clin. Pathol.*, **86**, 370–374 (1986).
16) Uchiyama, T., Yodoi, J., Sagawa, K., Takatsuki, K. and Uchino, H. Adult T-cell leukemia. Clinical and hematologic features of 16 cases. *Blood*, **50**, 481–492 (1976).
17) Cox. D. R. "The Analysis of Binary Data" (1970). Chapman and Hall, New York.
18) Harrell, F. E. The LOGIST procedure. *In* "SUGI Supplemental Library User's Guide," pp. 181–201 (1983). SAS Institute, Cary, NC.
19) SAS User's Guide. Statistics. (1982). SAS Institute, Cary, NC.
20) Kaplan, E. and Meier, P. Nonparametric estimation from incomplete observation. *J. Am. Stat. Assoc.*, **53**, 457–481 (1958).
21) Cox, D. R. Regression models and life tables. *J. R. Stat. Soc. Ser. B*, **34**, 87–220 (1972).
22) Harrell, F. E., Jr. The PHGLM procedure. *In* "SUGI Supplemental Library User's Guide," pp. 267–294 (1983). SAS Institute, Cary, NC.
23) Horning, S. J., Weiss, L. M., Crabtree, G. S. and Warnke, R. A. Clinical and phenotypic diversity of T cell lymphomas. *Blood*, **67**, 1578–1582 (1986).
24) Shimoyama, M., Ota, K., Kikuchi, M., Yunoki, K., Konda, S., Takatsuki, K., Ichimaru, M., Tominaga, S., Tsugane, S., Minato, K., Tobinai, K., Oyama, A., Hisano, S., Matsumoto, M., Takiguchi, T., Yamaguchi, K., Kinishita, K., Tajima, K. and Suemasu, K. Major prognostic factors of adult patients with advanced T-cell lymphoma/leukemia. *J. Clin. Oncol.*, **6**, 1088–1097 (1988).
25) Tobinai, K., Minato, K., Ohtsu, T., Mukai, K., Kogami, Y., Miwa, M., Watanabe, S. and Shimoyama, M. Clinicopathologic, immunophenotypic, and immunogenotypic analyses of immunoblastic lymphadenopathy-like T-cell lymphoma. *Blood*, **72**, 1000–1006 (1988).
26) Coiffier, B., Berger, F., Bryon, P-A. and Magaud, J-P. T-cell lymphomas: immunologic, histologic, clinical, and therapeutic analysis of 63 cases. *J. Clin. Oncol.*, **6**, 1584–1589 (1988).