Clinical Staging of Chronic Lymphocytic Leukemia

By Kanti R. Rai, Arthur Sawitsky, Eugene P. Cronkite, Arjun D. Chanana, Robert N. Levy, and Bernard S. Pasternack

A method of clinical staging of chronic lymphocytic leukemia (CLL) has been proposed which is based on the concept that CLL is a disease of progressive accumulation of nonfunctioning lymphocytes: stage 0, bone marrow and blood lymphocytosis only; stage I, lymphocytosis with enlarged nodes; stage II, lymphocytosis with enlarged spleen or liver or both; stage III, lymphocytosis with anemia; and stage IV: lymphocytosis with thrombocytopenia. Analysis of 125 patients in the present series showed the following median survival times (in months) from diagnosis: stage 0, >150; stage I, 101; stage II, 71; stage III, 19; stage IV, 19. The median survival for the entire series was 71 mo. The prognostic significance of the stage remained even after adjustment was made for age and sex. However, both sex and age were shown to be poor predictors of survival after adjustment for stage. The method of staging proved to be a reliable predictor of survival whether used at diagnosis or during the course of the disease. The proposed staging system was an equally accurate indicator for survival when applied to two other previously published studies of large series of patients.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a disease known to have a variable course; some patients die within 1 yr after diagnosis, while others live for longer than 10 yr. There are no generally accepted and measurable, standardized parameters available to a physician which might aid him in the assessment of prognosis of a patient with CLL either at the time of diagnosis or during the course of the illness. Dameshek[1] suggested that CLL is an accumulative disease of a functionally inactive population of lymphocytes. According to Dameshek, the CLL lymphocytes have a long life span, and, therefore, more and more such lymphocytes accumulate in a patient during the course of the disease. The observations of Boggs et al.[2] and Zippin et al.[3] reveal that, when the survival from the time of diagnosis is short, all the data obtained by physical examination and laboratory studies tend to be more abnormal at diagnosis than data found among the longer survivors. We propose a system for the clinical staging of CLL which is based on Dameshek's concept and have

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From the Division of Hematology, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. 11040, Medical Research Center, Brookhaven National Laboratory, Upton, N.Y. 11973, and the Department of Environmental Medicine, New York University Medical Center, New York, N.Y. 10016.

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The work described in this report was performed at the above noted institutions. It involved human patients who were treated in accordance with the precepts established in the Helsinki Declaration.

Address for reprint requests: Dr. Kanti R. Rai, Division of Hematology, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. 11040.

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tested its validity in predicting survival in a retrospective as well as prospective follow-up study of a large number of patients.

MATERIALS AND METHODS

Criterion for Diagnosis

The essential criterion for the diagnosis of CLL in this study was a sustained and absolute lymphocytosis in peripheral blood and bone marrow which could not be attributed to any other cause. Lymphocytes were of the small mature cell type. Patients known to have lymphosarcoma or lymphosarcoma cell leukemia were not included in the study. If adequate hematologic data at the time of diagnosis of CLL were available, patients were entered into this study without exception. The staging criteria were devised in 1968, and all patients who were alive then or who entered the study in the next 4 yr were observed on a prospective basis; all other follow-up data were obtained from a retrospective review of medical records.

Accrual of Patients, Sources, and Period

The diagnosis of CLL in our series, comprising 125 patients, was made between 1941 and 1971. The patients were seen either at the Medical Research Center of the Brookhaven National Laboratory or at the Long Island Jewish-Hillside Medical Center or by one of us in the private practice of hematology. The cut-off date for new patient entry into the study was December 31, 1971, and the common closing date for follow-up information was June 1, 1973.

Two other large series of patients reported in the literature[2,4] were also analyzed with respect to duration of survival from the time of diagnosis according to our proposed staging criteria (described below). The study of Boggs et al.[2] comprised 130 patients seen in Salt Lake City, Utah, between 1945 and 1964. Dr. Dane R. Boggs very kindly provided us with the raw data on this series of patients; adequate data at the time of diagnosis were available on 84 of these patients to allow us to "stage" their disease at diagnosis. Hansen[4] recently published a report based on 189 cases of CLL seen in Copenhagen between 1954 and 1963. Hansen's report includes extensive clinical data on all patients, and we were able to find 152 patients in this study whose data at diagnosis were adequate to allow us to "stage" them at diagnosis.

Clinical Observations

Symptoms related to CLL were recorded as (1) mild; only weakness; (2) moderate: weight loss, fever, night sweats, and pressure symptoms from large nodes, spleen, or liver; or (3) severe: shortness of breath, easy bruising, recurrent infections, and bleeding. Lymph nodes, spleen, and liver were considered to be enlarged if palpable on physical examination. No attempt was made in this analysis to separate the patients with massive organomegaly from those who had barely palpable enlargement of these organs.

The Proposed Criteria for Clinical Staging of CLL at the Time of Diagnosis

At clinical stage 0, the findings at diagnosis were lymphocytosis only, in blood as well as in bone marrow (absolute lymphocytes, 15,000/cu mm or more in blood, with 40% or more lymphocytes in the marrow). At clinical stage I, the findings at diagnosis were lymphocytosis with enlarged lymph nodes. At clinical stage II, the findings at diagnosis were lymphocytosis with enlarged spleen or liver or both. Nodes may or may not be enlarged. At clinical stage III, the findings at diagnosis were lymphocytosis with anemia (hemoglobin less than 11 g/100 ml or hematocrit less than 33%). Nodes, spleen, or liver may or may not be enlarged. No distinction was made with regard to the type of anemia, e.g., hemolytic or otherwise. At clincal stage IV, the findings at diagnosis were lymphocytosis with thrombocytopenia (platelet count less than 100,000/cu mm). Anemia and organomegaly may or may not be present.

Hematologic Methods

All hematologic tests were performed by the prevailing standard methods.[5] The method of platelet counting varied between the different institutions. The indirect method of calculating

the platelet count from the erythrocyte count and from the number of platelets per 1000 erythrocytes in the peripheral blood smear was used most often until the late 1950s. In the 1960s, all institutions gradually switched to the Brecher-Cronkite[6] phase-contrast method.

Cases of Initial Lymphocytosis of Less Than 15,000/cu mm

Included in our series also were 24 patients whose absolute lymphocyte count was less than 15,000/cu mm at the time of diagnosis (8–10,000 in four patients, 11–14,000 in 20 patients) and four patients (among these 24) whose marrow lymphocytes ranged between 28% and 40%. All these patients on follow-up examination eventually showed blood lymphocytosis of 15,000 or more and without any question had CLL as confirmed during the course of the disease.

Therapy—Criteria and Modalities

All patients in our series were treated according to conventionally accepted methods. Asymptomatic patients with stable disease activity did not receive any antileukemia therapy; when treatment was indicated, chlorambucil was most often the first drug of choice, and corticosteroids were added to therapy when anemia or thrombocytopenia was present or for fever ascribed to the disease activity. Radiation therapy to enlarged spleen or nodes was employed for discrete large masses or in the presence of local pressure symptoms. Some patients also received extracorporeal irratiation of blood (ECIB)[7] with or without other modalities of treatment. Vincristine, nitrogen mustard, and cyclophosphamide rarely were used.

Recording of Survival Duration and Change of Disease Stage

Duration of survival for our series was calculated from the date of diagnosis to date of death or the common closing date of June 1, 1973 for those patients still alive—none of whom were lost to follow-up. In the studies of Boggs et al.[2] and of Hansen,[4] closing dates for follow-up data were as described in their respective reports; in both of these series, patients lost to follow-up were considered alive until the date of last contact. Survival from change in disease (lower to higher number) was also separately determined for our series. When adequate follow-up data on patients were available to detect the change of stage during the course of the disease, such patients were restaged, and the survival duration from the time of entry into the new stage was noted.

Statistical Methods

The two-tailed t test was used for comparing patients in the different stages with respect to the mean age at diagnosis, incidence of symptoms, mean lymphocyte count in blood, and bone marrow lymphocyte percentage; differences between means were considered statistically significant if the p value was less than 0.05.

Survival curves for the three series were obtained by the product-limit actuarial method of Kaplan and Meier.[8] The survival curves were compared in their entirety by use of the chi-squared approximation to the conditional logrank test when more than two curves were involved.[9] For comparison of two survival curves, the Mantel[10] one-degree-of-freedom summary chi-square statistic was employed, since it yields a somewhat more precise p value than the chi-squared approximation based on the logrank test. Both of these methods[9,10] provided a significance test for evaluating differences in survival between (or among) groups of patients stratified by one factor while taking into account differences in distribution between the groups with respect to other factors thought to be associated with survival. In both methods, relative death rates were obtained for the subgroups being compared. The death rate for the whole group, i.e., the average for all patients combined, was described as 1.00. A subgroup with a prognosis worse than the average would have a relative death rate greater than 1, while a subgroup with a prognosis better than the average would have a relative death rate less than 1. (see Statistical Appendix). The factors considered in this study to be associated with survival in CLL and for which the aforementioned adjustments were made included sex, stage, and age at diagnosis (the latter was divided into four groups: ≤ 50, 51–60, 61–70, >70 yr).

Differences in survival said to be significant should be understood to mean statistically significant either at the 0.001, 0.01, or 0.05 probability levels (p values) which are indicated. All other differences having a p value greater than 0.05 are said to be nonsignificant (NS).

RESULTS

Clinical Data (Present Series)

One hundred twenty-five patients are included in our series; 46 were alive on the closing date, and 79 had died. The diagnosis was first made between 1941 and 1949 on four patients, between 1950 and 1959 on 26 patients, between 1960 and 1969 on 84 patients, and during 1970 and 1971 on 11 patients. The medical records on 65 patients were reviewed retrospectively, and 60 patients were clinically observed during the past 6 yr on a prospective basis.

The relevant clinical data of patients by each stage at the time of diagnosis are shown in Table 1. The following age differences were statistically significant: (1) the patients in stages 0, I, and II were younger than the stage III patients and (2) the stage 0 patients were younger than the stage IV patients. Although not shown in Table 1, the patients still alive were generally younger than those already dead (except in stage I in which the reverse was true). However, these differences were not significant at the 0.05 level. The mean lymphocyte level in blood of stage 0 patients was significantly lower than that of only stage IV; stage I mean lymphocyte count was not significantly different from any other stage, and stage II mean lymphocyte level was significantly lower than those of stages III and IV. Among the 24 patients whose lymphocyte count at diagnosis was less than 15,000/cu mm, 14 were in stage II, four were in stage 0, and two each were in stages I, III, and IV. The bone marrow lymphocyte ratio of stages 0 and II were significantly lower than that of stage IV.

Among patients in stage II at diagnosis, 92% had an enlarged spleen, 64% had an enlarged liver, 18% had enlargement of both organs, and 64% also had enlarged nodes. Among patients in stage III at diagnosis, 90% had enlarged nodes, and about 50% had enlarged spleen or liver; among stage IV patients, 70% had enlarged nodes, and about 50% had enlarged spleen or liver. One patient each in stages III and IV had neither nodes, spleen, nor liver palpable at diagnosis.

Table 1. Clinical Data of Patients According to Stage at Diagnosis (Chronic Lymphocytic Leukemia)

Stage at Diagnosis	No. of Patients	Per Cent Male	Mean Age at Diagnosis (Yr ± SD)	Per Cent Still Alive	Per Cent With Symptoms at Diagnosis (Severity)	Blood Lymphocyte Count × 10^{-3} (Mean)	Blood Lymphocyte Count × 10^{-3} (Range)	Bone Marrow Per Cent Lymphocytes (Mean)	Bone Marrow Per Cent Lymphocytes (Range)
0	22	28	54 ± 12	82	5 (mild)	25	(15–130)	52	(40–85)
I	29	59	57 ± 12	28	62 (mild)	42	(15–150)	63	(50–88)
II	39	82	57 ± 12	49	36 (mild to moderate)	38	(15–175)	61	(40–83)
III	21	57	66 ± 11	5	71 (moderate to severe)	78	(40–600)	79	(40–93)
IV	14	64	62 ± 8	0	100 (moderate to severe)	80	(15–190)	92	(60–93)
0 to IV	125	62	58 ± 12	37	50	40	(15–600)	63	(40–93)

Table 2. Data on Therapy Administered According to Stage at Diagnosis (Chronic Lymphocytic Leukemia)

Disease Stage at Diagnosis	No. of Patients	Mean Duration Between Diagnosis and Initiation of First Rx (yr)	Therapeutic* Agent Used During the Course of Disease	Per Cent of Patients Never Receiving Therapy
0	22	5.3†	C(8), P(3), RT(2), E(2)‡	59
I	29	2.8†	C(14), P(12), RT(4), E(4)‡ V(1), Cy(1)	21
II	39	1.6§	C(29), P(12), RT(14), E(5)‡ V(1), Cy(1), HN_2(1)	23
III	21	0.4	P(14), C(13), RT(5), E(3)‡	5
IV	14	0.3	P(9), C(9), RT(7), E(3)‡	0

*C, chlorambucil; P, prednisone or other corticosteroids; RT, local radiation to spleen or nodes; E, extracorporeal irradiation of blood; V, vincristine; Cy, cyclophosphamide; HN_2, nitrogen mustard. Number in parenthesis denotes number of patients so treated.

†When therapy was begun nearly all patients were in stage II, III, or IV.

‡With the exception of two patients who were in Stage II, all others were in Stage III or IV when E was used.

§With one exception: one patient first received therapy 17 yr after diagnosis.

The mean interval in years between the first diagnosis of CLL and the initiation of first anti-leukemia therapy is shown in Table 2; the therapeutic agents used and the percentage of patients who never received therapy are also detailed in Table 2. Therapy with ECIB, which was applied in 17 patients, deserves special comment. The rationale and method of this treatment have been published elsewhere.[7] At the time of this treatment 15 patients had already received other conventional agents and had either become nonresponsive to the agents or were in an advanced or terminal phase of stage III or IV of their disease. Only two patients who were in stage II at the time of ECIB had not received any other therapy previously, were recently diagnosed, and were in good clinical condition. Nearly two-thirds of the patients in stage 0 never received any therapy (Table 2); a majority of these patients were still alive and in our follow-up care and remained in either stage 0 or II, while two patients had progressed to stage IV at the closing date.

Duration of Survival

Overall survival and survival according to stage at diagnosis. The present series (125 patients), the data of Boggs et al. (84 patients), and the data of Hansen (152 patients) are represented in the panels A, B, and C, respectively, of Fig. 1 which shows overall survival as well as survival according to the stage of disease at diagnosis. The curve for stage 0 of the present series (Fig. 1A) is shown to end at 144 mo because, with the product-limit actuarial method, the cumulative per cent surviving is computed and plotted each time a death occurs; thus the last point on the curve represents the last observed death. Seven patients were still alive in this group at 144 mo. The duration of survival of every patient of the present series, dead or alive on the closing date, is shown in Fig. 2. Figure 1B shows only three patients in stage 0 in the series of Boggs et al., one alive at 24 mo, one lost to follow-up at 37 mo, and one alive at 116 mo. Therefore stage

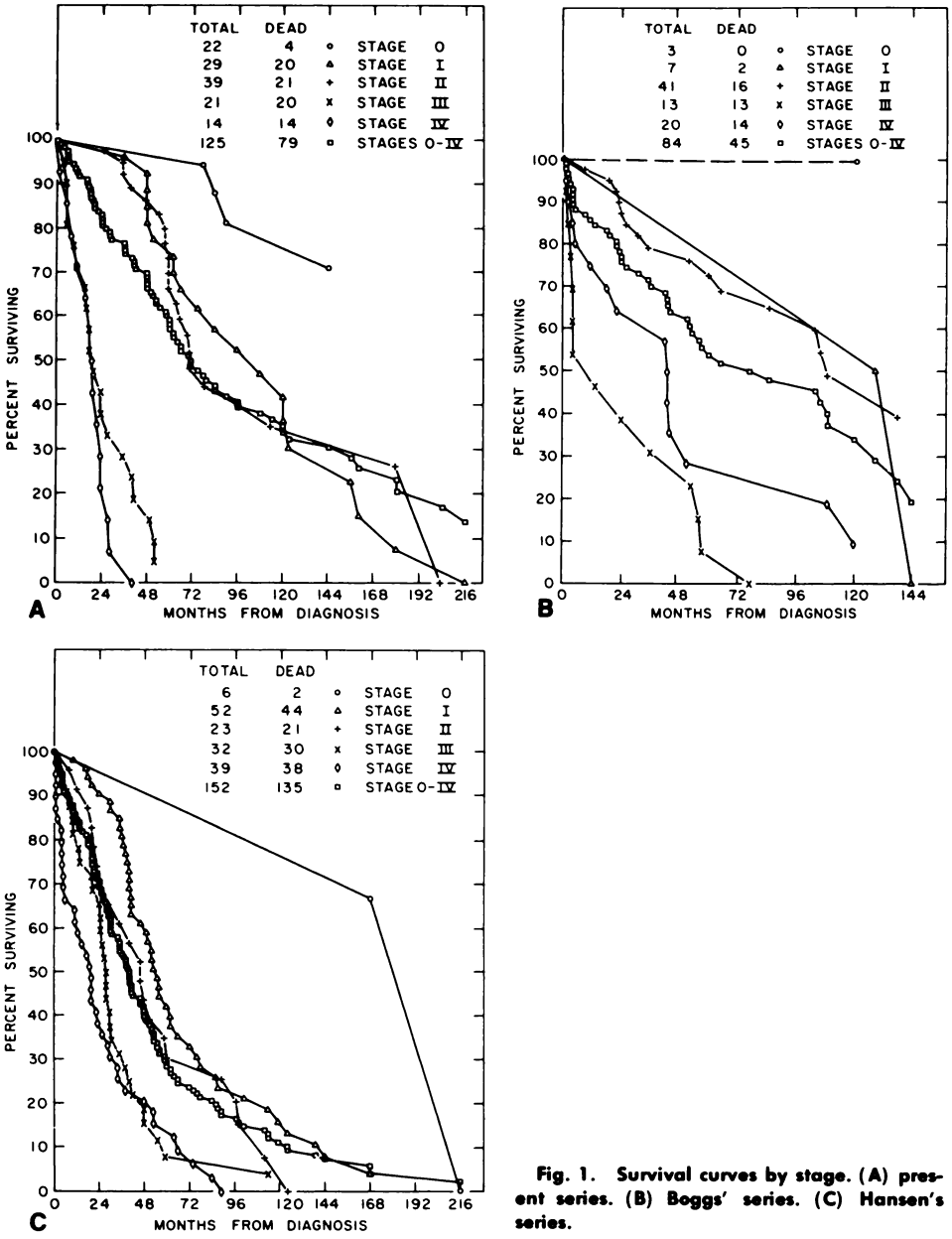

Fig. 1. Survival curves by stage. (A) present series. (B) Boggs' series. (C) Hansen's series.

0 is represented in Fig. 1B by a dashed straight line at 100% survival. The median survival times for the three studies are shown in Table 3.

Survival according to age at diagnosis and according to sex. Figure 3 shows survival curves for the three series by age at diagnosis. In the present series (Fig. 3A) survival appears to be poorer with advancing age; in the series of Boggs et al. (Fig. 3B) the age group of 51–60 yr appears to have a better survival than the younger age group, as is also the case in the series of Hansen (Fig. 3C).

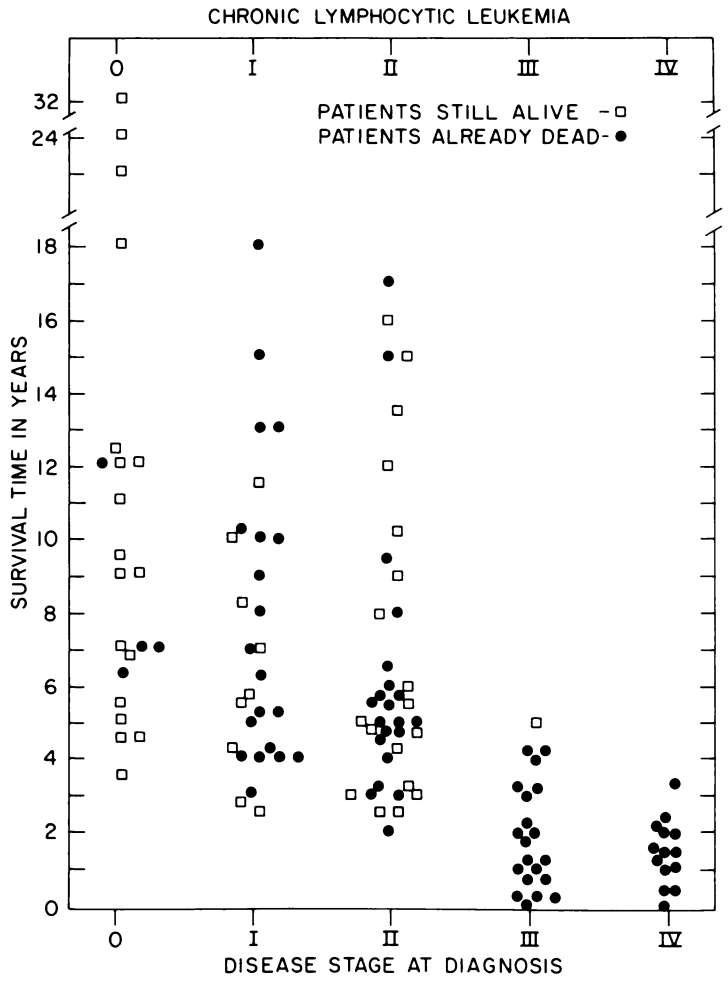

Fig. 2. Survival times by stage for dead and alive patients in the present series.

Table 3. Median Duration of Survival According to Stage at Diagnosis (Chronic Lymphocytic Leukemia)

Stage at Diagnosis	(A) Present Series		(B) Boggs et al.		(C) Hansen	
	No. of Patients	Median Survival (mo)	No. of Patients	Median Survival (mo)	No. of Patients	Median Survival (mo)
0	22	>150	3	—	6	180
I	29	101	7	130	52	60
II	39	71	41	108	23	47
III	21	19	13	9	32	26
IV	14	19	20	42	39	20
Overall	125	71	83	77	152	40

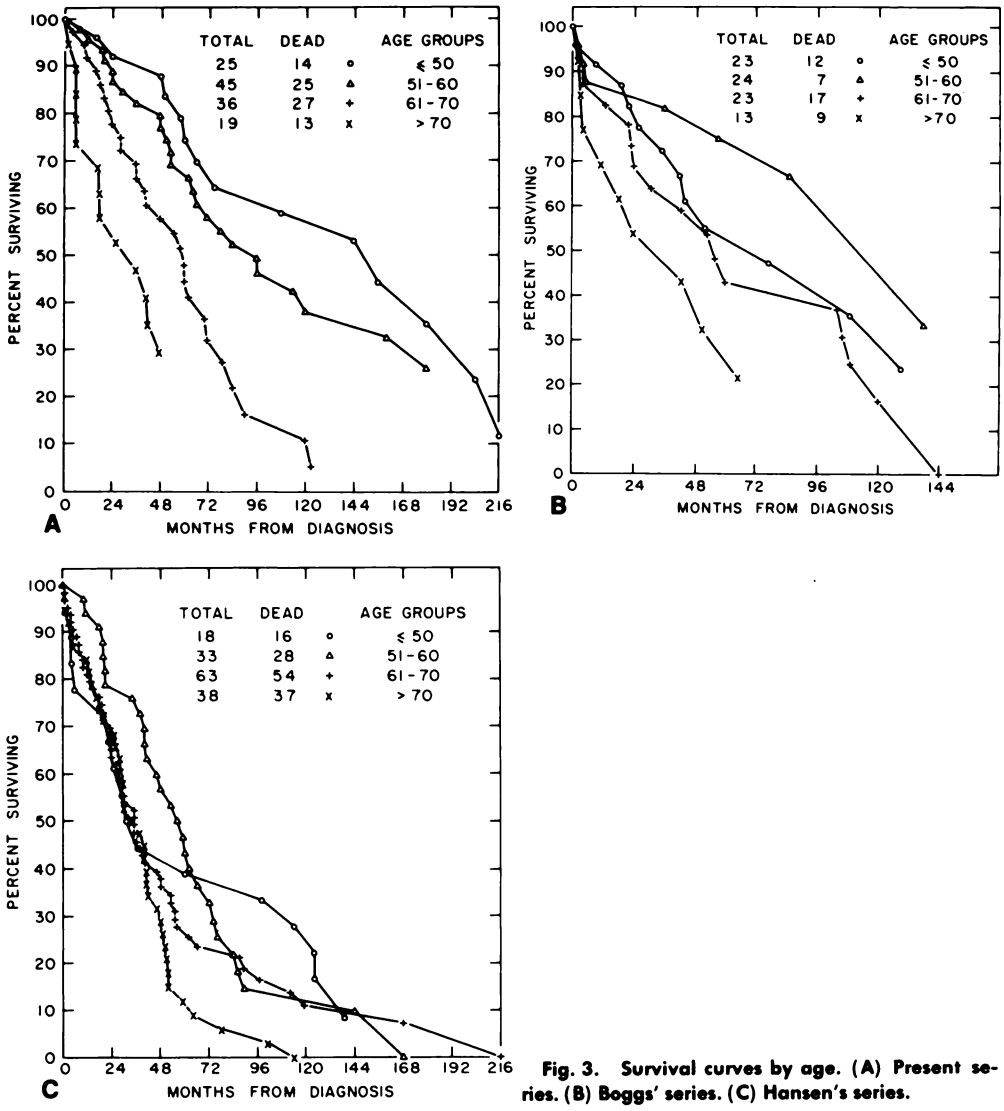

Fig. 3. Survival curves by age. (A) Present series. (B) Boggs' series. (C) Hansen's series.

Survival curves for the three series according to sex are shown in Fig. 4. Females appear to have a better survival in the present series (Fig. 4A) and in the series of Hansen (Fig. 4C), but there appears to be no difference in survival between males and females in the series of Boggs et al. (Fig. 4B).

Statistical analysis of survival data. When the survival curves of the five stages of each series (Fig. 1) were compared after adjustment for age and sex, the differences remained highly significant, as shown in Table 4. However, when the survival curves of the four age groups of each series (Fig. 3) were compared after adjustment for stage and sex, differences in the present series and in the series of Boggs et al. were no longer significant; in the series of Hansen, sig-

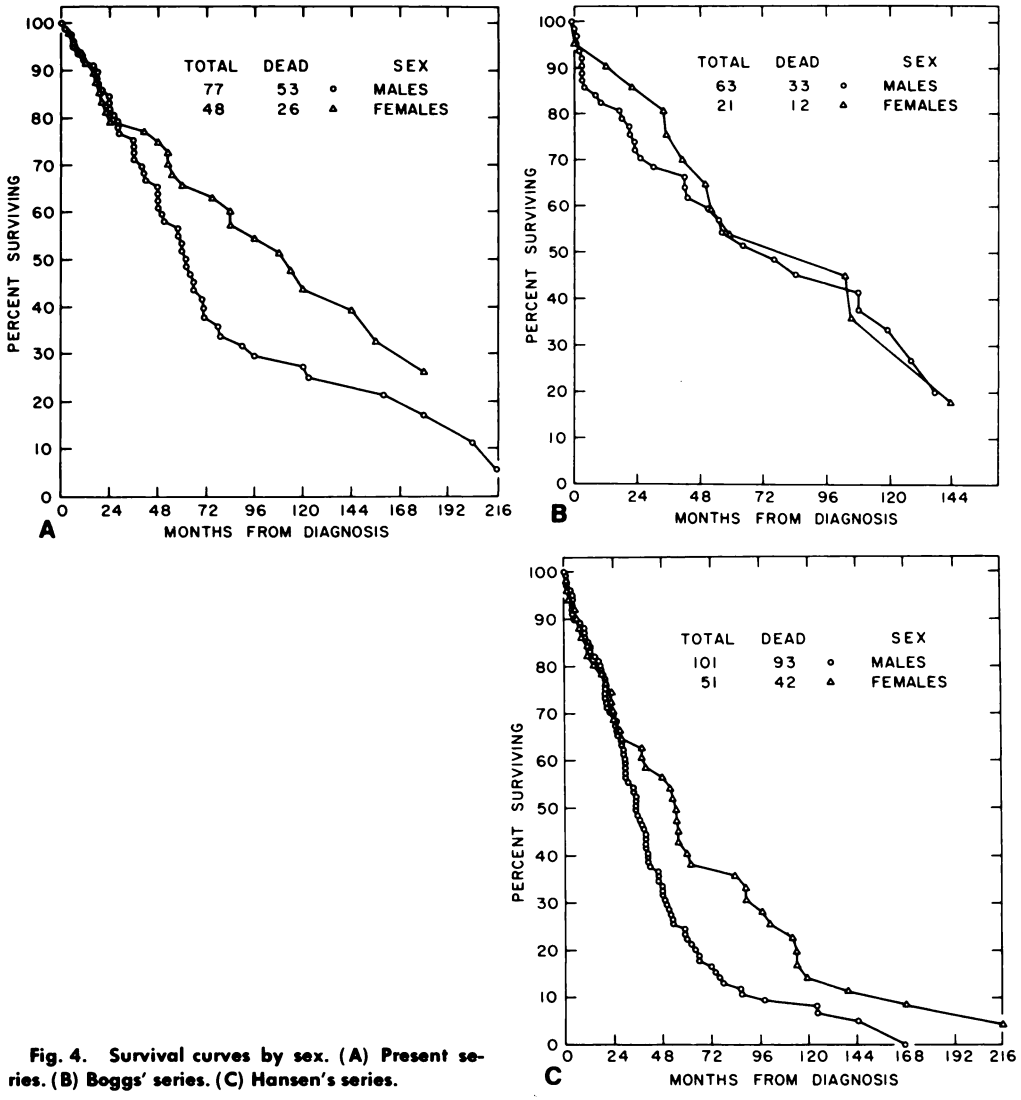

Fig. 4. Survival curves by sex. (A) Present series. (B) Boggs' series. (C) Hansen's series.

nificance was barely obtained ($p < 0.05$), as shown in Table 5. The survival curves according to sex (Fig. 4) were not found to be significantly different in any of the three series when adjusted for stage and age at diagnosis, as shown in Table 6.

Change of Stage During the Course of the Disease and Survival (Present Series)

In the present series, we had data on all patients during the clinical course of their disease, so it was possible for us to ascertain when a patient moved from one stage to another. For example, when a patient who was in stage I at diagnosis first showed evidence of enlargement of the spleen or liver, he was considered stage II at that time, and the duration of survival from that time to

Table 4. Survival From Diagnosis by Stage Adjusted for Age at Diagnosis and Sex

Stage at Diagnosis	N*	O	E	O/E	χ^2 (4 df) (p value)
(A) Data of present series					
0	22	4	17.51	0.23	49.63
I	29	20	21.57	0.93	($p < 0.001$)
II	39	21	27.24	0.77	
III	21	20	8.22	2.43	
IV	14	14	4.46	3.14	
All	125	79	79.00	1.00	
(B) Data of Boggs et al.					
0	3	0	1.06	0.00	20.90
I	7(1)†	1	3.64	0.27	($p < 0.001$)
II	41(2)	14	21.30	0.66	
III	13	13	4.69	2.77	
IV	20(1)	13	10.31	1.26	
All	84(4)	41	41.00	1.00	
(C) Data of Hansen					
0	6(2)	0	8.38	0.00	32.27
I	52(8)	36	54.30	0.66	($p < 0.001$)
II	23	21	20.68	1.02	
III	32	30	18.48	1.62	
IV	39(2)	36	21.16	1.70	
All	152(12)	123	123.00	1.00	

*N, number of patients in group; O, observed number of deaths in group; E, expected number of deaths based on survival for all patients; O/E, relative death rate. χ^2 (4 df), logrank test statistic which is approximated by chi-square with 4 degrees of freedom under the null hypothesis.

†Number in parenthesis denotes deaths not included in O due to inability to cross-match for sex, age, and duration of follow-up.

death or to the closing date (if the patient was still alive, irrespective of current stage) was entered into the survival data for patients changed to stage II. When that patient became anemic, the duration of survival from that point was entered into survival data for patients changed to stage III, and so on. The median duration of survival of patients originally in a stage at diagnosis, as well as the median survival of patients entering that stage from other stages can be seen in Fig. 5. Differences in survival time in any stage, whether a group of patients was diagnosed initially in that stage or the group entered the stage during the course of the disease, were not significant.

Among the patients in stages 0, I, and II (the stages with median survival times of 70 mo or longer), 50% of patients in stage 0 at diagnosis have remained in stage 0, 27% of stage I patients have remained in stage I, and 50% of stage II patients have remained in stage II at the closing date. The duration of follow-up is rather short for the patients in stages I or II at diagnosis who have so far not changed their disease stage (and therefore will not be detailed here); for the 11 patients in stage 0 at diagnosis who have remained in stage 0, the survival data are as follows: three patients, 3.5–6.0 yr; five patients, 7.0–12.5 yr; and one patient each at 18, 23, and 32 yr after diagnosis. These patients are also included in the 59% of stage 0 patients (Table 2) who have not been given any antileukemia therapy.

Table 5. Survival From Diagnosis by Age at Diagnosis Adjusted for Stage and Sex

Age at Diagnosis (yr)	N*	O	E	O/E	χ^2 (3 df) (p Value)
(A) Data of Present Series					
≤50	25(4)†	10	15.75	0.63	4.04
51–60	45(4)	21	22.65	0.93	(NS)
61–70	36(1)	26	20.56	1.26	
>70	19(1)	12	10.04	1.20	
All	125(10)	69	69.00	1.00	
(B) Data of Boggs et al.					
≤50	23(3)	9	9.60	0.94	1.64
51–60	24	7	9.78	0.72	(NS)
61–70	23(3)	14	12.61	1.11	
>70	13(1)	8	6.01	1.33	
All	83†(7)	38	38.00	1.00	
(C) Data of Hansen					
≤50	18(3)	13	18.72	0.69	8.03
51–60	33(4)	24	33.57	0.71	($p < 0.05$)
61–70	63(4)	50	43.07	1.16	
>70	38	37	28.65	1.29	
All	152(11)	124	124.00	1.00	

*N, number of patients in group; O, observed number of deaths in group; E, expected number of deaths based on survival for all patients; O/E, relative death rate. χ^2 (3df), logrank test statistic which is approximated by chi-square with 3 degrees of freedom under the null hypothesis.

†Number in parenthesis denotes deaths not included in O due to inability to cross-match for sex, stage, and duration of follow-up.

‡Does not include one patient whose age at diagnosis was not available.

Table 6. Survival From Diagnosis by Sex Adjusted for Stage and Age at Diagnosis

	N*	O	E	O/E	χ^2 (1 df) (p value)
(A) Data of Present Study					
Males	77(18)†	35	35.13	1.00	0.02
Females	48(4)	22	21.87	1.00	(NS)
All	125(22)	57	57.00	1.00	
(B) Data of Boggs et al.					
Males	63(17)	16	16.04	1.00	0.05
Females	21(3)	9	8.96	1.00	(NS)
All	84(20)	25	25.00	1.00	
(C) Data of Hansen					
Males	101(24)	69	61.58	1.12	3.08
Females	51(11)	31	38.42	0.81	(NS)
All	152(35)	100	100.00	1.00	

*N, number of patients in group; O, observed number of deaths in group; E, expected number of deaths based on survival for all patients; O/E, relative death rate; χ^2 (1 df), summary chi-square test statistic with 1 degree of freedom under the null hypothesis.

†Number in parenthesis denotes deaths not included in O due to inability to cross-match for stage, age, and duration of follow-up.

Stage 0	No.of Pts.	Med.Survival (Months)	Stage I	No.of Pts.	Med.Survival (Months)	Stage II	No.of Pts.	Med.Survival (Months)	Stage III	No.of Pts.	Med.Survival (Months)	Stage IV	No.of Pts.	Med. Survival (months)
at Dx	22	> 150	Changed to I	3	> 90	Changed to II	7	66.0	Changed to III	2	12.0	Changed to IV	6	13.2
			Stage I at Dx	29	101.1	Changed to II	10	46.0	Changed to III	10	14.0	Changed to IV	10	12.0
						Sum of above Changed to II	17	56.4	Changed to III	11	12.5	Changed to IV	13	13.3
						Stage II at Dx	39	71.0						
									Sum of above Changed to III	23	14.0	Changed to IV	10	5.0
									Stage III at Dx	21	19.0			
												Sum of above Changed to IV	39	12.0
												Stage IV at Dx	14	19.0

Fig. 5. Chronic lymphocytic leukemia. Comparison of median duration of survival according to stage of disease at diagnosis or to first observation of change in stage during follow-up.

DISCUSSION

In addition to the earlier report of Boggs et al.,[2] Zippin et al.[3] and Hansen[4] recently have provided excellent reviews of the literature concerning factors which may influence prognosis in CLL, and each one of these three reports also presented in-depth analyses of their respective series of patients. These studies[3,4] confirmed the observation of Boggs et al.[2] that all physical and laboratory evidences of disease at diagnosis tended to be more severe among patients with short survival time than was the case among the longer surviving patients. The recent studies[3,4] indicated a significantly better prognosis for women and younger people than for men and older people, respectively, although Boggs et al.[2] observed no relationship between survival and sex and only a slight correlation between survival and age at diagnosis. As the following discussion will reveal, we believe these discrepancies are only apparent because they disappear when the proposed staging scheme is used.

The clinical characteristics of patients comprising the present series are summarized in Tables 1 and 2. The male: female ratio was 1.6: 1, and the mean age at diagnosis was 58 yr. The incidence of symptoms did not correlate with survival. The shorter surviving group had a higher incidence of organomegaly than the long-term survivors. We recognize that, when the liver was noted to be palpable in a patient's record in the group reviewed retrospectively, it did not necessarily establish that the liver was enlarged, but we have no reason to question such an observation. The total lymphocyte count in blood and the bone marrow lymphocyte percentage tended to be higher at diagnosis among the shorter surviving groups than was the case for the long-term survivors. The long-surviving groups had a greater proportion of patients who never received any antileukemia therapy, and they also had a longer interval between diagnosis and start of such therapy, but the choice of agents used among the long- or the short-survivor groups was not different. From our study we cannot tell whether the poor prognosis for patients in stages III and IV was because of the greater amount of therapy given to them or because of the natural history of the disease.

The clinical staging proposed and tested in this analysis represents a stepwise increase in the physical and laboratory evidence of the disease, from mere lymphocytosis of stage 0 to enlargement of lymph nodes in stage I, enlargement of spleen or liver in stage II, and thereafter progressive compromise of bone marrow function as revealed by anemia in stage III and thrombocytopenia in stage IV. A large majority of stage IV patients were also anemic, although none of stage III patients were thrombocytopenic. It should be noted that the criteria of anemia and thrombocytopenia as set forth in this staging system include only the relatively severe forms (hemoglobin less than 11 g/100 ml, platelets less than 100,000/cu mm). All criteria proposed (although arbitrary) are objective and readily measurable.

As can be seen from Fig. 2 (the present series), all stage IV patients died within 3.5 yr from diagnosis, and only one patient in stage III has lived to 5 yr. In stages II, I, and 0, there was a progressively larger proportion of patients still alive, and overall survival was clearly longer. The longest survivors of the

entire series were the three patients in stage 0 who were alive at 23, 24, and 32 yr after diagnosis.

The association of stage at diagnosis with survival in the present series is evident from Figs. 1A and 2. Age and sex also appear to be significant prognostic factors, as indicated in Figs. 3A and 4A. When the five stages are arranged in ascending numerical order from 0 to IV, there is a continuously decreasing survival as one proceeds from stage 0 to IV even after adjusting for age and sex. Table 4(A) shows the relative death rate (O/E) increasing from 0.23 for stage 0 patients to 3.14 for stage IV patients ($p < 0.001$). Conversely, when survival is compared by age at diagnosis after adjustment for stage and sex, differences apparent in Fig. 3A almost disappear. Table 5(A) shows a slight increase in the relative death rate with age at diagnosis, but the differences are statistically not significant. Similarly, differences in survival by sex disappear entirely after adjustment for stage and age at diagnosis (Table 6(A)). Thus, the analysis of this series strongly suggests that our proposed staging criteria are predictive of length of survival, whereas sex and age at diagnosis are factors which do not play as important a role in determining prognosis as heretofore believed.

In order to validate our proposed method of staging as an indicator of prognosis for survival, we applied our staging criteria to two other series reported in the literature, viz., Hansen[4] and Boggs et al.[2] The unadjusted survival curves by stage at diagnosis for these two series of patients were comparable to those of our own series, as evidenced by Fig. 1. The observed differences in survival according to stage for these two series remained highly significant ($p < 0.001$) after adjustments were made for age at diagnosis and sex (Table 4). This observation was in agreement with our own results. When these series were analyzed by age while controlling for stage and sex (Table 5), the differences in survival were not statistically significant for Boggs' data and just significant for the data of Hansen ($p < 0.05$). Comparison of observed and expected deaths by sex after adjustment for stage and age revealed no difference in either of the two series (Table 6), again confirming our own findings.

Figure 1 and Table 3 show that overall survival in the series of Hansen was poorer than in the other two series. This difference may partly be ascribed to the fact that Hansen's series contained a higher percentage of patients in stages III and IV than did the other two series. Also, perhaps the frequency and extent of therapy of patients in Hansen's series might have been different from the other two series. It will be observed from Fig. 1 and Table 4 that in each of the three series examined there were essentially three, rather than five, groups which differed with respect to survival: stage 0, stages I and II, and stages III and IV. We would nonetheless suggest that for future follow-up and treatment the five stages be maintained apart for the following reasons: (1) From the concept of CLL being an accumulative disease, the concept on which the present staging has been proposed, enlargement of nodes without hepatosplenomegaly and hepatosplenomegaly with or without nodes ought to reflect different degrees of accumulation of lymphocytes—and perhaps in the future may be treated by different therapeutic schedules. (2) Similarly, anemia without thrombocytopenia and thrombocytopenia with or without anemia reflect different degrees of compromise of marrow function and possibly of body burden of

lymphocytes and of the overall biology of the disease. Perhaps, again in the future, different lines of treatment may be indicated. (3) It is always possible in the future to redesign the staging into three groups; nothing will be gained at this time by doing so, and important prospective follow-up data may be lost by combining stages I and II and stages III and IV now.

We believe (Fig. 5) our initial observations indicate that there is a pipeline-like progression of disease, and the outlook for survival for a patient is essentially the same whether he is found to be in a stage at diagnosis or enters that stage from an earlier stage during the course of the disease. However, a close follow-up of a larger number of patients on a prospective basis is needed to confirm this observation. It is noteworthy that, in our series, among the surviving patients in stage 0 at diagnosis who have so far remained in stage 0, a large majority has been followed for more than 7 yr, and none has received antileukemia therapy. Clinical staging of CLL should therefore prove useful in identifying the patients in stage 0 who need not be exposed to cytotoxic agents, considering that in stage 0 the disease remains uniquely nonprogressive for a very long time. It might be advisable for future invesitgators to record the results of new therapeutic measures separately for each stage rather than to consider all patients with CLL as a homogeneous population with respect to the expected duration of survival.

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STATISTICAL APPENDIX

As an illustration, the steps used to evaluate differences in survival among the five stages adjusting for sex and age using the logrank test can be described as follows: (1) divide the survival time from diagnosis of the patients into 1-yr periods, (2) for each age-sex combination (eight since there are four age groups within each sex) construct a 5 x 2 contingency table for each 1-yr period of followup; the i-th table for the series of tables representing a specific age-sex combination can be characterized as

Stage	No. Dying	No. Alive	Total
0	A_{0i}	B_{0i}	N_{0i}
I	A_{1i}	B_{1i}	N_{1i}
II	A_{2i}	B_{2i}	N_{2i}
III	A_{3i}	B_{3i}	N_{3i}
IV	A_{4i}	B_{4i}	N_{4i}
All	M_{1i}	M_{2i}	T_i

(3) calculate the expected number of deaths for each stage subgroup for the i-th table, e.g., for stage III $[E(A_{3i}) = N_{3i}M_{1i}/T_i]$, (4) sum the observed and expected numbers of deaths over all contingency tables (each series within each age-sex combination and then over all age-sex combinations—denote by O, the summed observed deaths, and by E, the summed expected

deaths), and (5) compute the logrank test statistic

$$\Sigma(O - E)^2/E$$

where the summation is over all stages; this statistic is approximately distributed as chi-square with four degrees of freedom (the degrees of freedom for the chi-square is always one less than the number of subgroups being compared with each other) under the null hypothesis—there is no difference in survival among stages.

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