Survival in Chronic Lymphocytic Leukemia

By Calvin Zippin, Sidney J. Cutler, William J. Reeves, Jr., and Diana Lum

Survival of 839 chronic lymphocytic leukemia patients has been reviewed in relation to a number of patient and disease characteristics. Over-all, the relative 5-yr survival rate was 44%. Studying survival by age and sex led to the following observations: Dividing age into intervals < 50, 50–59, 60–69, 70–79, and 80 yr and over, relative survival declined with increasing age; relative 5-yr survival for females was higher than that for males–50% versus 41%. This pattern of superior survival of females over males was noted in all but one of the age intervals. Survival was negatively associated with the presence of recorded clinical signs and symptoms, hematological abnormalities, and pathological bone marrow findings. Differences in survival were also found by treatment category and interval from diagnosis to initiation of treatment. Adjustment for differences in distribution of each of these variables did not materially diminish the survival differences noted by age and sex. An unexpected pattern of survival in relation to white blood count level was noted. Survival increased with increasing white blood count at diagnosis, peaking in the interval at 25,000–49,000, and decreasing after that. When survival by white blood count was adjusted for some variables which were found to be associated with survival, the gradient was still noted, though somewhat reduced.

THE PRESENT PROJECT was undertaken to study survival in chronic lymphocytic leukemia as related to a number of patient and disease characteristics. The study group consisted of 839 patients with chronic lymphocytic leukemia diagnosed between 1955 and 1964 in 24 hospitals participating in the End Results Program of the National Cancer Institute. Information recorded in this study included signs and symptoms, hematologic and bone marrow data, treatment, and survival time from diagnosis. Included are variables previously reported as associated with prognosis in this disease.[1-6]

MATERIALS AND METHODS

Records on all patients diagnosed with chronic lymphocytic leukemia during the period 1955–1964 in the institutions listed in the Appendix were reviewed. Previously untreated patients whose hematologic and bone marrow findings were consistent with chronic lymphocytic leukemia and who did not have a previously proven diagnosis or history of lymphosarcoma were included in the present study. The cutoff date for follow-up information was 1969, which represented a

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minimum of 5 yr and a maximum of 14 yr from time of diagnosis. Follow-up information at 5 yr after diagnosis was available for 92% of the patients. The data were collected in a retrospective review of medical records.

The general plan of the study was similar to that in the study of acute lymphocytic leukemia,[7] also using data from hospitals participating in the End Results Program of the National Cancer Institute. The recording of data was done by the staff of the local institution (i.e., medical record personnel, tumor registrars, or physicians), following detailed study instructions. Editing, including consistency checks and coding of data, was carried out in the General Tumor Registry, Cancer Research Institute, University of California, San Francisco.

RESULTS

Race, Sex, and Age

Of the 839 patients in the study, 798 (95%) were white, 30 (4%) were Negro, 4 (0.5%) were Oriental,* and race was not recorded in 7 cases (0.8%). Male cases (549) exceeded females (290) in the ratio of 1.9 to 1.

Five age intervals (<50, 50–59, 60–69, 70–79, 80+ yr) were employed in this study. As shown in Table 1 the age distributions of males and females were quite similar. The median ages were 68.1 and 67.7 yr for males and females, respectively. Nine per cent of males and 7% of females were under age 50. Twelve per cent of males and 9% of females were over 80. For both sexes combined, median age was 68.0 yr; mean age, 66.5 yr.

The observed 5-yr survival rate for the total study group was 34%. Figure 1 shows relative survival curves for males, females, and both sexes combined. The 5-yr relative survival rate,[8] which adjusts observed survival[9] for expected mortality from other causes, is higher for females (50%) than for males (41%). For both sexes combined it is seen to be 44%.

Table 1 gives 5-yr relative survival by age group and by sex. Females had consistently better survival than males between ages 50 and 79, which included approximately 80% of cases of each sex. For each sex relative survival decreased with increasing age. Under age 50, the survival results were similar for each sex. Males did better than females over age 80. In the age interval 50–59

Table 1. Frequency Distributions and 5-yr Survival Rates from Time of Diagnosis by Age and Sex

	Age Distribution						5-yr Relative Survival Rates (%)		
	Numbers			Percentages					
Age (yr)	Males	Females	M + F	Males	Females	M + F	Males	Females	M + F
< 50	51	20	71	9	7	8	56 (7)*	57 (12)	57 (6)
50–59	101	57	158	18	20	19	48† (6)	67† (7)	56 (4)
60–69	165	85	251	30	30	30	38 (5)	49 (6)	42 (4)
70–79	164	100	264	30	34	31	31 (5)	40 (6)	35 (4)
50–79	430	243	673	78	84	80	38† (3)	51† (4)	43 (2)
80 +	68	27	95	12	9	11	37 (12)	21 (14)	32 (9)
All ages	549	290	839	99	100	99	41 (3)	50 (4)	44 (2)

*SE in parentheses.

† Sex difference significant at 5% level.

*1 Chinese, 1 Japanese, 1 American Indian, 1 unspecified other.

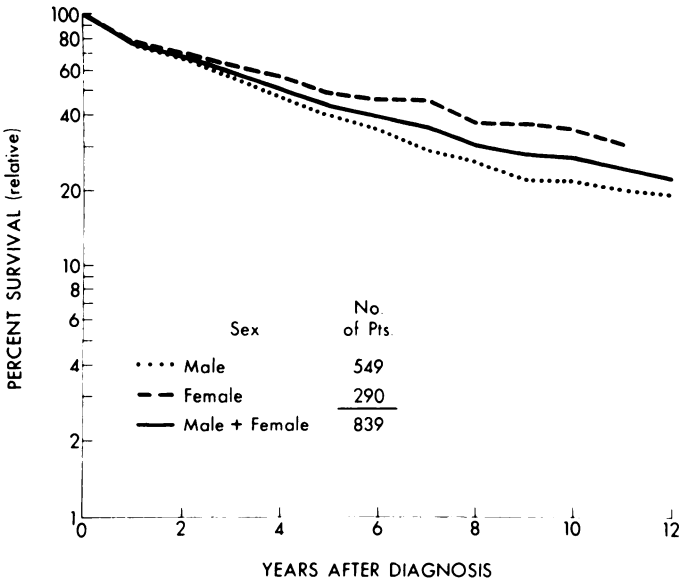

Fig. 1. Relative survival curves by sex.

as well as the grouped interval 50–79, survival of females was significantly better ($p < 0.05$) than for the corresponding group of males.

In the remaining sections of this paper we shall look at survival in relation to a number of patient and disease characteristics. Since the concentration of cases falls into the interval 50–79 yr of age, we shall, in each instance, summarize findings for this age interval by sex. We shall then attempt to assess whether favorable or unfavorable distributions of variables associated with prognosis might help explain the observed differences in survival by age and by sex.

Clinical Signs and Symptoms

Table 2 provides by sex for the age interval 50–79 yr, the relative frequency distributions and survival results in relation to the presence or absence, at time of admission to the reporting institution, of a number of clinical signs and symptoms, i.e., bleeding, infection, disability, lymphadenopathy, and organomegaly. In most instances, females showed superior survival in comparison with males both when a condition was recorded to be absent as well as when present. Exceptions were noted in the presence of organomegaly or severe disability.

The differential survival between females and males was greater in the absence of any clinical sign than in its presence. Significant differences at the 1% level were observed in the absence of bleeding, infection, and any organomegaly, whereas in the presence of any sign, none of the differences in survival between sexes was statistically significant.

For each sex the prognosis was poorer in the presence of each condition than in its absence. The survival gradient in relation to the presence or absence of a clinical sign was more distinct for females than for males. Among females, survival decreased significantly ($p < 0.05$) in the presence of bleeding, disability, and any organomegaly. In contrast, among males survival was significantly re-

Table 2. Relative Frequency Distributions and 5-yr Relative Survival Rates by Clinical Sign or Symptom and by Sex, Ages 50–79

Clinical Sign or Symptom	Percentages		5-yr Relative Survival (%)	
	Males	Females	Males	Females
Bleeding				
Present	17	21	34 (7)*	36 (8)
Absent	82	79	40† (3)	55† (4)
Not recorded	0	‡	§	‡
Total	99	100	38¶ (3)	51¶ (4)
Infection				
Present	23	23	36 (6)	43 (8)
Absent	77	77	39† (3)	53† (4)
Not recorded	0	‡	§	‡
Total	100	100	38¶ (3)	51¶ (4)
Disability				
Severe	16	15	27 (7)	16 (7)
Mild	44	42	32 (4)	45 (6)
None	25	25	55 (6)	70 (7)
Not recorded	15	18	42 (8)	63 (9)
Total	100	100	38¶ (3)	51¶ (4)
Any lymphadenopathy				
Present	72	60	36 (3)	46 (5)
Absent	12	19	38 (9)	54 (9)
Not recorded	16	21	51 (8)	61 (9)
Total	100	100	38¶ (3)	51¶ (4)
Any organomegaly				
Present	64	60	37 (4)	37 (5)
Absent	30	35	42† (6)	74† (6)
Not recorded	6	5	41 (12)	49 (17)
Total	100	100	38¶ (3)	51¶ (4)

* SE in parentheses.
† Sex difference significant at 1% level.
‡ n = 0.
§ Survival rate not computed for n < 5 cases.
¶ Sex difference significant at 5% level.

duced solely in the presence of disability and not for the other variables studied.

Since the relative frequencies of most of the conditions shown in the table are quite similar for males and females, the over-all superior survival of the females relative to males cannot be attributed to more favorable distributions of the characteristics among the females as might be confirmed by a statistical adjustment* for such differences. Similarly statistical adjustment for differences in

*The largest difference between males and females is noted for "any lymphadenopathy" for which 72% of males and 60% of females were found to be positive. When 5-yr relative survival rates were standardized to the over-all relative frequency distribution of this characteristic in males plus females combined in the age interval 50–79 yr, standardized rates were 50% and 39% for females and males, respectively, as compared with 51% and 38%, noted previously in

Table 3. Relative Frequency Distributions and 5-yr Relative Survival Rates by Treatment, Interval between Diagnosis and Treatment, and Sex, Ages 50–79

	Percentages		5-yr Relative Survival (%)			
	Males	Females	Males		Females	
Treatment						
Chemotherapy only	30	19	45	(6)*	60	(9)
Steroids only	7	10	19	(9)	35	(11)
Chemotherapy and steroids	7	13	21	(9)	42	(10)
Radiation with/without other	21	26	31	(6)	36	(7)
Total treated	65	68	35	(4)	43	(4)
No treatment	27	24	44†	(6)	64†	(8)
No information	8	8	47	(11)	73	(13)
Total	100	100	38†	(3)	51†	(4)
Interval from diagnosis to treatment						
Treated within 4 mo	46	51	31	(4)	32	(5)
Not treated within 4 mo	38	34	49‡	(5)	76‡	(6)
Treated after 4 mo	17	14	43‡	(7)	80‡	(9)
Not treated to date of last follow-up	21	20	54†	(7)	75†	(8)
Not treated, survival time less than 4 mo	5	4	§		0	
No information	10	11	50	(10)	71	(11)
Total	99	100	38†	(3)	51†	(4)

*SE in parentheses.

† Sex difference significant at 5% level.

‡ Sex difference significant at 1% level.

§ Not computed due to aberrant effect of cases lost to follow-up on survival calculation and where all observed deaths occurred within 5 yr.

the relative frequency of the clinical signs does not alter the decreasing survival pattern by age or the superior survival of females over males within individual age intervals noted earlier.

Treatment and Interval from Diagnosis to Treatment

Patients were classified according to initial course of therapy which, for patients receiving any treatment prior to the time of this report, included modalities employed within a 4-mo period from the time of initiation of treatment. Initial forms of therapy were categorized as chemotherapy only, steroids only, chemotherapy plus steroids, and radiation with or without another form of therapy. Approximately one-fourth of each sex group (Table 3) received no treatment to the time of this study. Thirty per cent of males and 19% of females received chemotherapy only. Twenty-one per cent of males and 26% of females received radiation therapy either alone or in combination with other forms of therapy. Steroid therapy only or chemotherapy plus steroids was received by smaller percentages of patients.

Over-all, the best results for both males and females were experienced by those either not receiving therapy to time of study or those whose initial course of treatment was chemotherapy only. In females significantly ($p < 0.05$) poorer

Table 1. Thus even adjustment for differences in relative frequency of "any lymphadenopathy" does not contribute materially to explaining the superior survival of females over males in the age interval 50–79.

survival was found among those receiving either steroids alone or radiation compared with the no treatment group. Males receiving steroids also had significantly poorer survival than either the no treatment or chemotherapy group. In the case of both males and females those treated by steroids apparently had more severe disease than other treatment groups in terms of hematological criteria for severity. There were no statistically significant differences between males and females in any of the treatment groups. However, females not receiving definitive treatment had a significantly ($p < 0.05$) superior survival than males not receiving definite therapy.

Table 3 also provides for each sex data on interval from diagnosis to initiation of treatment as well as relative 5-yr survival. Patients were classified into two groups: those treated within 4 mo of diagnosis and those not treated within this interval after diagnosis. Somewhat fewer females were untreated during the first 4 mo following diagnosis than males (34% versus 38%). A longer interval before first treatment was significantly ($p < 0.05$) associated with better survival, especially among the females. Among males those treated subsequent to 4 mo after diagnosis had a poorer 5-yr relative survival from time of diagnosis (43%) than those known to have had no treatment initiated later than 4 mo after diagnosis (54% relative 5-yr survival). Among females, little difference was noted.

Five-year relative survival rates for males and for females were similar among those treated within 4 mo. Among those treated after a longer interval than 4 mo following diagnosis, there is a marked superiority ($p < 0.01$) in survival of females over males.

Standardizing for differences in time between diagnosis and treatment does not decrease the over-all difference in survival between the sexes. Similarly, the age differential in survival within sex continues to be seen when adjustment is made for time until treatment is started.

Hematological Findings

Hematological and/or bone marrow studies were carried out on all patients in this study and the findings were used as a basis for confirmation of the diagnosis. For the purpose of this report only findings from hematological studies carried out within 2 mo of diagnosis and recorded in the patient's medical chart were employed. Forty-five per cent of the patients age 50–79 were diagnosed prior to admission to one of the participating institutions. As a result, information on platelet counts, hematocrits, and lymphocyte levels at time of diagnosis was recorded with varying degrees of completeness. For these hematological variables, it is therefore not possible to arrive at definitive associations with survival. However, as would be expected, there is the suggestion from the limited data available of an increase in survival with increasing values of platelet count and hematocrit level, and a decrease in survival with increasing percentage of lymphocytes.

The distributions of white blood counts (Table 4) for males and females were quite similar. It is interesting to note that for both males and for females, the highest survival is seen in the white blood count interval 25,000–49,000. In the case of males, survival in this interval is just slightly above that for the interval

Table 4. Relative Frequency Distributions and 5-yr Relative Survival Rates by White Blood Count and Sex, Ages 50-79

White Blood Count (x 10^3)	Percentages		5-yr Relative Survival (%)			
	Males	Females	Males		Females	
<10	4	6	16	(10)*	30	(13)
10-24	21	21	47	(7)	43	(8)
25-49	26	27	49†	(6)	69†	(7)
50-99	16	17	37	(7)	40	(9)
100+	24	19	26	(5)	35	(8)
Not recorded	10	10	36‡	(9)	77‡	(11)
Total	101	100	38†	(3)	51†	(4)

*SE in parentheses.
† Sex difference significant at 5% level.
‡ Sex difference significant at 1% level.

of 10,000-24,000. The superior survival in the white count interval 25,000-49,000 is most dramatic in the case of females for whom the 5-yr relative survival in that interval is 69% compared to 43% ($p < 0.05$) in the next lower level. This observation is explored further in the Discussion Section of the paper.

Other than for the white blood count interval of 10,000-24,000, survival of females was better than that of males in the various intervals. Survival of females was significantly better ($p < 0.05$) than that of males in the interval 25,000-49,000. It should also be noted in Table 4 that white blood counts at time of initial diagnosis were not recorded for 10% of both males and females. The survival of males with unknown white blood count was similar to the over-all survival of the total group of males. However, the survival of females with unknown white blood counts was higher than that experienced by those in any white blood count interval and was significantly higher ($p < 0.01$) than that for males whose white blood counts were not recorded.

Standardization of the distribution of white blood cell counts did not diminish either the survival gradient between males and females in the age interval 50-79, or the survival pattern by age within sex.

Bone Marrow Findings

Although the information on bone marrow cellularity was recorded for less than half the study group, those with hypercellular marrow had poorer survival than those with marrows categorized as normal or hypocellular. Similarly, although not recorded for approximately one-third of the patients in the study, those with over 65% of lymphocytes in the marrow showed a poorer survival than those with less extensive lymphocytic infiltration.

DISCUSSION

The over-all five-yr observed survival from diagnosis for the total group of patients was 34%. For comparison, Osgood[10] and Boggs et al.[2] reported survival results from Oregon (January 1, 1941 through June 30, 1954 diagnoses) and Utah (January 1, 1945 through June 30, 1964 cases) of 37% and 54%, respectively. The better survival results from Boggs' study may be due to age differ-

ences between study groups and the result of superior treatment methods. However, in the absence of controlled clinical trials to assure comparability of patient groups, this cannot be documented scientifically. In addition, references have been made to the possibility that at least several forms of the disease exist with long survival noted for those patients with the "benign" form.[5,6] The possibility of different distributions of the various forms of the disease in groups studied for survival may also contribute to the reported disparity in survival results.

In the present study survival was observed to be associated with age and sex. Survival declined with increasing age among patients in their 50s, 60s, and 70s. Females had superior survival to males over-all and within each of these decades of age.

Survival was noted to be negatively associated with the presence of clinical signs and symptoms (bleeding, infection, poor performance status, lymphadenopathy, and organomegaly), hematological abnormalities (low platelets, low hematocrit, high peripheral blood lymphocyte count), and pathological bone marrow findings (hypercellular bone marrow and high lymphocyte level). Adjustment for differences in distribution of each of these variables individually did not reduce materially the survival differences by age and sex noted above. The female advantage in survival was less in the presence than in the absence of any of these individual clinical signs and symptoms listed above. This pattern was not observed for either the hematological or bone marrow characteristics.

Differences in survival were also noted by treatment category and time interval between diagnosis and time of initiation of treatment. Adjustment for differences in the distribution of this interval explained neither the survival differences by treatment nor the age and sex differences in survival.

Perhaps the most surprising survival pattern was found in relation to white blood count level at time of diagnosis in that the best survival for each sex was noted for those with white blood counts in the interval 25,000–49,000. Studying this further, it was observed that patients with counts between 25,000 and 49,000 had the highest percentage able to carry out their normal activities. Nevertheless, as shown below, adjustment for differences in performance status distribution between white blood count groups did not materially reduce the superior survival for those in the interval 25,000–49,000.

	White Blood Cell Count ($\times 10^3$)				
	<10	10–24	25–49	50–99	100+
Percentage with no disability (based on those with information only)	19	33	38	28	21
5-yr relative survival (%) for those with information on disability status	25	45	57	37	29
Adjusted 5-yr relative survival (%) (adjusted for disability status)	31	44	55	36	32

Survival from time of diagnosis is longer for those whose treatment was initiated more than 4 mo after diagnosis than for those treated within 4 mo. The distribution of intervals between diagnosis and treatment was reviewed in relation to white blood count at time of diagnosis. As seen below, the percentage untreated within 4 mo was highest in the interval 25,000–49,000.

	White Blood Cell Count ($\times 10^3$)				
	<10	10–24	25–49	50–99	100+
Percentage untreated within 4 mo (based on those with information only)	29	53	61	34	11
5-yr rel. surv. (%)	25	46	56	39	30
Adjusted 5-yr relative survival (%) (adjusted for interval between diagnosis and treatment)	26	40	52	39	30

However, adjustment for the differences in distribution of time until treatment by white blood count interval did not change the relationship between survival rate and white blood count interval.

Combining data on disability status and interval until treatment, the table below shows that those with no disability and with white blood counts between 25,000–49,000 had the highest percentage initially treated more than 4 mo after diagnosis. For both the no disability and mild disability groups, a gradient between percentage not treated within 4 mo and white blood count is observed with the peak recorded for the white blood count interval of 25,000–49,000. For those with severe disability, a less consistent pattern was noted. In spite of these interesting observations, when survival by white blood count is adjusted for both disability status and time until treatment, a gradient is still noted although somewhat diminished, with the best survival again found for the white blood count interval 25,000–49,000, as shown below.

Percentage Distributions of Times Until Treatment by Disability Status and by White Blood Cell Count, Both Sexes Combined, Ages 50–79

Disability Status	Interval Between Diagnosis and Treatment	White Blood Cell Count ($\times 10^3$)				
		<10	10–24	25–49	50–99	100+
		Percentages				
None	Treated within 4 mo	50	41	20	58	89
	Not treated within 4 mo	50	59	80	42	11
Mild	Treated within 4 mo	67	53	48	57	85
	Not treated within 4 mo	33	47	52	43	15
Severe	Treated within 4 mo	86	41	65	100	97
	Not treated within 4 mo	14	59	35	0	3

	White Blood Cell Count ($\times 10^3$)				
	<10	10–24	25–49	50–99	100+
5-yr relative survival (%) for those with information on disability status and time until treatment	28	46	56	36	30
Adjusted 5-yr relative survival (%) (adjusted for disability status and time until treatment)	34	40	52	36	34

To this point then, we have not been able to adequately explain the survival pattern in relation to white blood count which we have observed. Similarly, we have not been able to account for the differences in survival between the sexes or the inverse gradient of survival with age. It is possible that refine-

ments in disease classification as well as clinical and laboratory findings which would be available for a more recent series of cases could help contribute to an explanation of our observations.

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APPENDIX

LIST OF STUDY HOSPITALS

Harbor General, Torrance, Calif.
Los Angeles General, Los Angeles, Calif.
Los Angeles Tumor Institute, Los Angeles, Calif.
Merritt, Oakland, Calif.
Mount Zion, San Francisco, Calif.
St. Francis, Lynwood, Calif.
St. Mary's, San Francisco, Calif.
San Francisco General, San Francisco, Calif.
University of California at San Francisco, Calif.
White Memorial, Los Angeles, Calif.
Hartford, Hartford, Conn.
St. Raphael, New Haven, Conn.
Waterbury, Waterbury, Conn.
Yale-New Haven, New Haven, Conn.
University of Chicago, Chicago, Ill.
University of Iowa, Iowa City, Iowa
Charity, New Orleans, La.
Massachusetts State Department of Health, Boston, Mass. (3 hospitals)
University of Michigan, Ann Arbor, Mich.
New York Medical College, New York, N.Y.
Albert Einstein, Philadelphia, Pa.
University of Virginia, Charlottesville, Va.