Expectancy for Life in Chronic Lymphatic Leukemia

By ROBERT A. GREEN AND HUBERT DIXON

There are wide discrepancies in published data on survival in chronic leukemia, and it is not clear what the real prospects for survival are in this group of diseases. We have impressions of a variable chronicity, but there is need for standards if the results of new methods of treatment are to be meaningful, and it is important to know how valid the standard series are. Obvious reasons, in terms of selection and methods of analysis, account for some of the discrepancies. The largest of the reference series, that of Tivey published in 1954, has served as a baseline for most subsequent comparisons. The data in another large series reported in 1960 by Feinleib and MacMahon differ widely from Tivey's. The results reported by Osgood differ from both of these and were in fact, superior to any results reported to date.

The analysis of 125 cases of chronic lymphatic leukemia reported in this paper was originally undertaken for purposes of comparing survival in a series treated in an unprogrammed manner by conventional methods, with the survival in Osgood's series in which all patients were treated by the structured program of titrated, regularly spaced total-body irradiation. When these results were compared with the reference series noted above, differences in survival were so striking that it also seemed worthwhile to consider how such marked differences could be explained.

Material

A. Selection

The patients reported here represent a fairly typical cross section of chronic leukemia patients seen in a University Clinic and Hospital. They represent all cases of chronic lymphatic leukemia diagnosed in the University of Minnesota Clinics and Hospitals from July, 1945 to July, 1957 and followed for an additional 4 years, to July, 1961. At the time of cut off (July, 1961) 97 (77 per cent) patients had died, 25 (21 per cent) were living, and 2 were lost to follow up. No patient, living or dead, was excluded for any reason whatever from the series, and deaths from all causes are included. Patients lost to follow up are included, being considered as alive at the time of last observation.

B. Diagnosis

The diagnosis in every case was established on morphologic grounds, either by the findings of typical peripheral morphology in the presence of characteristic clinical findings, by bone marrow biopsy, or both. All morphologic diagnoses were established by review of blood and/or bone marrow preparations in the Special Hematology Laboratory under the supervision of Dr. Dorothy Sundberg.

At some time during the course of their illness, 118 of the 125 patients were considered leukemic in terms of peripheral blood counts and morphology. Five were considered subleukemic and two aleukemic.
C. Characteristics

The mean age for the total of this group is 62 years. Males predominate in a ratio of 1.9 to 1. The economic status varies. Age, sex, economic status, and many other factors have been related to survival experience in leukemia, but generally speaking no significant relationships have been established for these categories, and no attempts have been made to correlate these factors with survival in this study.

D. Treatment

With the exception of a few patients treated for variable periods by Osgood's method, the majority were treated only when, in the opinion of the clinician, symptoms of their leukemia required it. For this reason, a certain number of patients were entirely untreated for their leukemia except in some cases by transfusion and other supportive measures. Twenty-two of the ninety-seven who died and 13 of the 25 living patients were untreated for leukemia. Of the former, 17 died of causes other than leukemia and five were reported by their local physicians to have died of leukemia.

The 13 untreated living patients are mostly long survivors, 54 to 128 months. The living patients who were treated are also long survivors, 59 to 239 months. Without doubt, the influence of these patients on survival of the whole series is great and may be the principal reason why survival in this series is so much greater than in the reference series.

A number of different clinicians participated in their management over the 16-year period and a variety of agents were used. Forty-eight patients were treated with conventional deep x-ray, but half of these also received some other form of treatment including P32, corticosteroids, and alkylating agents. Nine patients were treated by Osgood's method, but all of these also had some other form of treatment at some time during the course of their illness. In regard to this method, we concluded that if it is to be used successfully, the clinician must be thoroughly familiar with the details of the method, and preferably, that the same clinician should follow these patients regularly. Thirty-two patients were treated with corticosteroids, usually for complications such as hemolytic anemia or thrombocytopenia and not as primary treatment. Twenty-nine were treated with other agents including nitrogen mustard, (16), TEM (5), cyclophosphamide (1), or chlorambucil (6). Because of the small numbers in each group and because the majority had more than one type of treatment, it was not considered feasible to compare survivals according to the type of treatment. Judging from the wide range and form of distribution of survival in chronic leukemia, it is obvious that large numbers of cases are needed in any category to permit valid conclusions as to the efficacy of any type of treatment.

Methods of Evaluating Survival Data

The variability of survival in chronic leukemia poses several problems which cannot be treated adequately by conventional statistical methods. One of the problems in this type of chronic malignant disease is that survival times extend over a wide range, from a few weeks to many years. In the series reported here, for example, the shortest survival was 3 weeks and the longest nearly 20 years. Not only does the distribution of survival extend over many years, but the survival times are not distributed normally, being quite markedly skewed. The arithmetic mean of such nonnormal distributions does not represent the midpoint in the series, and the standard deviation or variance are useless as parameters to describe this type of distribution. The question of how to deal statistically with living patients (an incomplete series) without waiting for them all to die also has to be considered. Two statistical methods which meet the various requirements of this type of distribution have been used in the analysis of this series. They are a modified maximum likelihood method of logarithmic probability analysis and an actuarial method.

The maximum likelihood method as proposed by Fisher,5 Boag,6 and Lea7 was used by Tivey1 and by Osgood.3,4 Feinleib and MacMahon2 used an iterative modified maximum likelihood method and Feinleib8 devised a short cut for this. These methods predict with reasonable accuracy the survival at any interval for patients in an incomplete series. They
are approximate methods and depend on the assumption that distributions of survival in this disease follow a log-normal distribution. That is, although the frequency distribution of the actual survival times is markedly skewed, the logarithms of the survival times have an approximately normal distribution.

There are no exact procedures with which we can calculate maximum likelihood estimates of the parameters of the distribution when the followup data is incomplete. Elveback\(^9\) circumvented this problem by using the actuarial method of Berkson and Gage\(^10\) in which probabilities and estimates of survival times are not dependent upon any assumptions concerning the form of the survivorship distribution.

The data in this series have been analyzed in detail by this method and by the Feinleib short-cut method. They are reported in terms of survival both from the date of onset and from the date of diagnosis. There are objections to reporting survival from date of onset because of uncertainties in determining this accurately by backdating from the history. Much of the data in the literature, however, is reported in terms of survival from onset, and Osgood has stated that in his series total duration gives better prediction of results than time after first therapy. Both Tivey and Feinleib and MacMahon found that the duration of survival after diagnosis is independent of the duration of symptoms prior to diagnosis, but the meaning of this is not entirely clear.

**RESULTS**

The survivorship functions calculated by the actuarial method for the 125 patients in this series are shown in the curves in figure 1. By interpolating on the survivorship curves of figure 1 the estimated median survival times (the time at which 50 per cent of the patients are still alive) with a standard error of .045, are 47.8 months from onset of symptoms and 40.8 months from diagnosis.

The Feinleib short cut application of the modified maximum likelihood method results in a 3 parameter log-normal distribution. In this modified method the third parameter, a constant, \(a\), is subtracted from the survival time in order to improve the goodness of fit of the observed distribution to the maximum likelihood solution. In the formulation, the variable \(t\) is a standard normal variate with mean zero and variance one, \(x\) is the survival measured
Fig. 2.—Duration of survival from date of diagnosis for 125 patients with chronic lymphatic leukemia. Duration of survival in months plus 1.6 is plotted along logarithmic scale.

from onset or diagnosis, as the case may be, a is the constant, and log b is the mean, and c the standard deviation of the variable log (x-a).

With the date of onset as the starting point for these 125 patients, we get the following estimates:

\[ a = -1.60 \]
\[ \text{Mean} = \log b = 1.7011 \]
\[ \text{S.D.} = c = .5078 \]

From the graph of the log-normal distribution in figure 2, we get a median survival time from onset of approximately 48 months.

Using the date of diagnosis as a starting point we get the estimates:

\[ a = -1.66 \]
\[ \text{Mean} = \log b = 1.6131 \]
\[ \text{S.D.} = c = .5511 \]

From the graph in figure 3, we get a median survival time after diagnosis of 39 months.

DISCUSSION

The data presented here differ radically from the survival data of the two much larger reference series, those of Tivey\(^1\) and of Feinleib and MacMahon.\(^2\) They more nearly resemble the results reported by Osgood\(^3,4\) which at the time of their publication were clearly superior to any results reported in the literature. The comparative figures are presented in table 1.

In Tivey's series of 1978 collected cases reported in the literature from 1925 to 1951, the median survival after onset of symptoms for both types of chronic leukemia was 2.65 years (table 1). The figure for 685 patients with chronic
Fig. 3.—Duration of survival from date of onset of symptoms for 125 patients with chronic lymphatic leukemia. Duration of survival in months plus 1.6 is plotted along logarithmic scale.

Lymphatic leukemia was 2.77 years. The median survival time after beginning therapy was 1.70 years for 325 cases of chronic lymphatic leukemia. These figures have served since their publication in 1954 as the major baseline for comparing survivals in other series of chronic leukemia.

Survivals in Tivey's material are significantly longer than those reported by Feinleib and MacMahon, in whose study the median survival after onset for 541 cases of both types of leukemia was 1.53 years. Median survival after diagnosis for 649 cases was .97 years. The duration of survival in chronic

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*Median Survival - Beginning of Therapy to Death
lymphatic leukemia and chronic myelogenous leukemia was not significantly different.

In Osgood's series of 163 cases treated by the method of titrated, regularly spaced total-body irradiation the median survival from onset was 4.3 years for both types, and 5.16 years for 102 cases of chronic lymphatic leukemia. The median survival from first therapy was 2.83 years for all cases and 3.75 years for chronic lymphatic leukemia (table 1).

The survival time in the 125 patients with chronic lymphatic leukemia in the present series was 4 years from onset and 3.25 years from diagnosis calculated by the Feinleib short cut method (table 1). Calculated by the actuarial method, the values are 3.98 years and 3.4 years, respectively. The differences in survival reported in this study and in the two reference series are much too great to be accounted for by chance alone. They can't be explained on the basis of differences in the methods of analysis, since methods have been used in this study comparable to those used in the others and in Osgood's series. The differences must somehow be explained on the basis of differences in selection of the material. These differences may be due to selective influences of some kind which operate to some extent in any series. In the group reported in this paper, perhaps the major selective influence is that all cases were seen in a University referral clinic, yet it is this type of material which is probably most commonly studied and reported. Short lived cases are not necessarily excluded and it is quite possible that better and earlier diagnoses are made in this kind of series. Several factors of selection are noted in the material reported by Tivey which are not present in this series. Cases were deleted for a variety of reasons in some of his groups whereas in the present study no cases were deleted. Furthermore, many of the patients included in Tivey's collected series were treated prior to 1941 and, therefore, prior to the antibiotic era. In the present study all cases were treated during the antibiotic era and many also since corticosteroids became generally available for treatment of serious complications.

The discrepancies between the present study and that of Feinleib and MacMahon are even more striking, and the factors influencing them somewhat different. There is an obvious difference in the selection of cases, all in this study having been seen in one institution, whereas the Feinleib-MacMahon material includes all cases in various hospitals in Brooklyn on whom hospital records could be located. Both are incomplete series (both living and dead patients included), although in their material only .6 per cent of the patients were still living and in this study 21 per cent of the patients were still living at the cut-off date. In their series 9.4 per cent of the patients were lost to follow up and 2 per cent were lost to follow up in this series.

The main differences seem to be due to long periods of survival in the living patients in this series and to the large early loss from death in the Feinleib-MacMahon material. In their series, 18 per cent had a total duration of survival after onset of less than 6 months, and 35 per cent total duration of survival of less than 1 year. In this study only 3.2 per cent survived less than 6 months.
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from onset and 12.8 per cent less than 1 year. In the Feinleib-MacMahon series 9 per cent of patients survived longer than 5 years and in this series 32.8 per cent survived longer than 5 years. Although some of the discrepancy seems to be due to disproportionate number of short survivors in the Feinleib-MacMahon material, it could also be explained in part by a greater number of late diagnoses and by the fact that some of their cases were first diagnosed at autopsy when survival times had to be considered as zero.

The material and survival data for this series more nearly resemble those reported by Osgood. In a group of 100 cases of both types of chronic leukemia treated by his method, only 5 per cent survived less than 6 months, 11 per cent less than 1 year, and 32 per cent longer than 5 years.

The results recorded in the above survival data may be related, apart from differences in therapy, to the composition of the groups being compared. The diagnosis of chronic lymphatic leukemia obviously does not in itself confer homogeneity on these groups. Chronic lymphatic leukemia is a disease with a very wide clinical spectrum, at one end of which are patients diagnosed early in the course of their disease, and long surviving patients with mild disease. At the other end are patients diagnosed late in the course of their disease, some not until at autopsy, and short surviving patients with severe disease. It has been suggested from the discussion above that the reason for the differences in survival figures for the series being reported and the reference series of Tivey and particularly that of Feinleib and MacMahon is mainly one of differences in the composition of the groups reported. It is also quite possible that the similarity of survival data between the present series and the Osgood series is due to greater similarity in composition of these groups.

SUMMARY

Survival data were calculated for 125 patients with chronic lymphatic leukemia seen at the University of Minnesota Hospitals during the years 1945 to 1957 and followed for another 4 years. An actuarial method and modified maximum likelihood method were used for the statistical analyses.

The survival times in this study are significantly longer than those reported previously in large reference series of chronic leukemia. They more nearly approximate the results reported by Osgood for patients treated by his method of total body irradiation. It is suggested that in a disease with a wide clinical spectrum such as chronic lymphatic leukemia, differences in survival may be mainly related to differences in the composition of the groups being studied.

SUMMARIO IN INTERLINGUA

Datos de longevitate esseva calculate pro 125 patientes con chronic leucemia lymphatic vidite al Hospitales del Universitate Minnesota durante le annos 1945 a 1957 e tenite in observation durante quatro annos additional. Le analyses statistic esseva execute per medio de un methodo actuarial e un modificate methodo de probabilitate maximal.

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longe que illos previemente reportate in extense series de casos de leucemia chronic. Illos es plus tosto simile al resultatos reportate per Osgood pro pacientes tractate per su metodo de irradiation del corpore total. Es proponite que in un morbo con un extense spectro clinic (como chronic leucemia lymphatic lo es), differentias de supervivencia sia reguardate como explicable primarimente per differentias in le composition del gruppos investigate.

REFERENCES

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