Prognosis of chronic lymphocytic leukemia as determined by peripheral blood smear and bone marrow findings

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THE PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA AS DETERMINED BY PERIPHERAL BLOOD SMEAR AND BONE MARROW FINDINGS

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INTRODUCTION

It is the purpose of this paper to determine if a relationship exists between the initial peripheral blood smear and bone marrow findings and the eventual prognosis of a patient with chronic lymphocytic leukemia. In this paper prognosis refers to the length of survival of the patient.

Since chronic lymphocytic leukemia is fairly common in older patients and is compatible with life for a relatively long time, an effort will be made to determine if such a patient's survival can be predicted with any degree of accuracy.

The information for this study is derived from the hematology files of the Department of Internal Medicine and the Tumor Survey at the University of Nebraska College of Medicine. This series includes patients who were known to have chronic lymphocytic leukemia and who were followed during their clinical course. This covers a time interval from 1950 to 1963.

Each patient was evaluated as to age at diagnosis, sex and race, date of diagnosis, associated diagnoses, first symptom to consultation, consultation to diagnosis, diagnosis to first treatment and the type of treatment used. Data on the peripheral blood smear was limited.
to analysis of the hemoglobin, total white blood cell count, reticulocytes and platelets. The bone marrow was studied for its relative cellularity, gross evaluation of plasma cells and percentage of cells in the lymphocytic series.

DIAGNOSTIC INFORMATION

Of the total 64 cases, 42 were males and 22 were females. This is a ratio of approximately two males to one female. Sixty-two of these cases were white and two were Negro.

The mean age at the time of diagnosis was 67.0 years with the men having a mean age of 68.0 years and the women having a mean age of 65.1 years. The oldest patient in this series was 87 years and the youngest was 38 years. Almost 40% of the patients were in the eighth decade (70-79). This is graphically represented by figure 1.

![Graph showing age at diagnosis of chronic lymphocytic leukemia in 64 cases.](image)

Fig. 9. Age at Diagnosis of Chronic Lymphocytic Leukemia in 64 cases.
At the present time 44 of these patients have died while 20 are still living. The patients that died survived an average of 3.20 years after the onset of symptoms and 2.76 years after the diagnosis of chronic lymphocytic leukemia was confirmed. Ten of these patients died of diseases that were probably not directly related to the leukemia. That is, seven of them died of carcinoma and three of them from a myocardial infarction. The longest survival in this group was nine years and 11 months while the shortest was one week.

However, the 20 patients that are still living already have lived an average of 5.22 years after the onset of symptoms and 4.51 years after the confirmation of a diagnosis of chronic lymphocytic leukemia. The longest survivor has already had symptoms for 15 years while the most recent case has had symptoms about 3 months.

When the whole group of 64 patients is analyzed, a mean value of 3.85 years is arrived at as the length of survival or duration of the illness after the onset of symptoms. A mean value of 3.31 years is the corresponding period of time after a positive diagnosis was made. Figure 2 represents a graphic illustration of these findings.

It is this mean value of 3.31 years that the various blood findings will be compared. However, since 20 of these patients are still living, it is obvious that the
mean value is only an absolute minimum for the length of survival. As these patients continue to live this figure will become larger.

Fig. 2. Duration of illness in 64 patients with chronic lymphocytic leukemia from the onset of clinical symptoms.

In evaluating this series of patients as to their prognosis the laboratory studies at, or as close to the time of diagnosis as possible, were studied. In all cases, however, at least some laboratory data was recorded before treatment was started. Some of the specific blood and bone marrow values were not available for each patient. As these particular values are encountered, this will be noted. Conclusions will be based only upon the available evidence.
PERIPHERAL BLOOD SMEAR

A hemoglobin value was available on each of the 64 patients. These values ranged from a low of 3.7 Gm. % to a high of 16.7 Gm. % with a mean of 11.5 Gm. %. Figure 3 is included to try and show some relationship between the initial hemoglobin value and the patient's length of survival after diagnosis.

Fig. 3. The Gm. % of hemoglobin in 64 patients with chronic lymphocytic leukemia as compared to the length of survival after diagnosis.
A value for the white blood cell count was also obtained on all 64 patients. The lowest count at or near the time of diagnosis was 4,100 per cu. mm., and the highest count was 576,000 per cu. mm. with a mean value of 82,200 per cu. mm. Figure 4 is used to show the relationship of the white blood cell count to the length of survival after diagnosis.

Fig. 4. White blood cell counts in 64 patients with chronic lymphocytic leukemia as compared to the years of survival after diagnosis.
A differential white cell count was available on 56 patients at or near the time of diagnosis. A mean value for the percentage of cells in the lymphocytic series was 81%. The vast majority of the cells were mature lymphocytes or smudge cells. Only occasionally was a prolymphocyte or lymphoblast present in the peripheral smear.

The percentage of reticulocytes was recorded in 38 patients at or near the time of diagnosis. The lowest value was 0.2% and the highest value was 6.3% with a mean of 1.4%. The normal reticulocyte response was considered to be between 0.5% and 1.5%. The percentage of reticulocytes is compared to the patient's duration of chronic lymphocytic leukemia after diagnosis by figure 5.

Fig. 5. Reticulocytes (%) in 38 patients with chronic lymphocytic leukemia as compared to the years of survival after diagnosis.
An indication of the number of platelets in all 64 patients was available at or near the time of diagnosis. However, in about one-half of the patients only a gross indication of the number present was recorded. That is, a note was made that the platelets were normal, increased or decreased. In the remainder of the patients an absolute value was given. Figure 6 shows the relationship of the number of platelets to the years of survival after diagnosis. The normal platelet count in the peripheral blood was assumed to be 150,000-600,000 per cu. mm.

Fig. 6. Number of platelets per cu. mm. in 64 patients with chronic lymphocytic leukemia as compared to the years of survival after diagnosis.
BONE MARROW FINDINGS

Because of the importance in diagnosis of chronic lymphocytic leukemia, the bone marrow findings at or near the time of diagnosis were studied in 58 patients. In six of the patients enough marrow fragments were not obtained to be of diagnostic value.

The degree of cellularity in the initial bone marrow was recorded for 54 of the patients in this series. The degree of cellularity was stated as being hypocellular, moderately cellular (normal), slightly hypercellular, moderately hypercellular or markedly hypercellular.

Figure 7 shows the relationship of the degree of cellularity to the years of survival after diagnosis.

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Fig. 7. The degree of cellularity in 54 patients with chronic lymphocytic leukemia as compared to the years of survival after diagnosis.
The number of plasma cells in the initial bone marrow was also evaluated in an effort to correlate it with the length of survival after diagnosis. A plasma cell determination was available on only 30 of the patients in this series. The results were listed as being decreased, normal or increased in number. The normal number of plasma cells in the bone marrow is considered to be 0.0-2.0 per cu. mm. However, the plasma cells were considered to be decreased if none were found on the bone marrow examination. Figure 8 shows the relationship of the number of plasma cells in the bone marrow and the years of survival after diagnosis.

![Graph showing the relationship of plasma cells in bone marrow to years of survival after diagnosis.]

Fig. 8. The plasma cells in the bone marrow of 30 patients with chronic lymphocytic leukemia as compared to the years of survival after diagnosis.
The percentage of cells of the lymphocytic series in the bone marrow at or near the time of diagnosis was recorded for 58 patients in this series. Most of the cells were mature lymphocytes with a few prolymphocytes and an occasional lymphoblast. The lowest percentage of cells in the lymphocytic series was 10% in one patient while four patients' marrows were 100% replaced. The calculated mean value was 66.2% for the entire series of patients. Figure 9 shows the relationship between the percentage of cells of the lymphocytic series and the length of survival after diagnosis.

Fig. 9. The percentage of cells of the lymphocytic series in the bone marrow of 58 patients with chronic lymphocytic leukemia as compared to the years of survival after diagnosis.
TREATMENT

Because of the multiple forms of treatment used on most patients, it is difficult to show any correlation between the length of survival and treatment with any specific agent. A tabulated list of treatments shows that some form of X-ray therapy was used in 34 patients, triethylenemelamine in 26 patients, chlorambucil (Leu­keran) in seven patients, phosphorus$^{32}$ in four patients, nitrogen mustard in one patient, aminopterin in one patient, cortisone in one patient, prednisone in one patient, iodine$^{131}$ in one patient, supporting therapy in six patients and no therapy in six patients.

DISCUSSION

In this study of 64 patients with chronic lymphocytic leukemia the mean age was determined to be 67.0 years. The mean survival time after diagnosis was calculated to be 3.31 years. According to the U.S. Bureau of the Census, the average person may expect to live 13.1 years$^{10}$ after reaching the age of 67 years. Therefore, it would appear that chronic lymphocytic leukemia had a marked effect upon the patient's expected survival. However, in order to state that this was statistically significant a control group of patients would be necessary.
In a series of 137 patients studied by Shimkin the mean age of onset was 54.3 years. This is considerably lower than the mean age of 67.0 years in this series. His mean survival from the time of diagnosis to death was 3.5 years. He found that the initial leukocyte count failed to have any correlation with the length of survival.

The longest mean survival time was reported by Osgood in a series of 102 patients with chronic lymphocytic leukemia who were treated with phosphorus. He determined that the mean survival time was about seven years. However, this was only estimated by the "method of maximum likelihood" which was applied to his study by Tivey. The latter author has shown that survival times in leukemia follow logarithm-normal distributions. Therefore, if one plots the length of time that a patient has had leukemia on log paper, he can estimate the length of his expected survival. This method of determining survival rates was not used in this study. Admittedly however, it would probably have given the final conclusions more validity.

In one of the largest series reported Tivey studied 1,978 patients with chronic lymphocytic or granulocytic leukemia. He demonstrated that there was no difference
between the survival prospects of patients with lymphocytic and patients with granulocytic leukemia. He showed that half of the patients will die in about 2.65 years after onset of the first clinical symptoms and that 10% will live seven years after the onset of the disease while 1% will survive 15 years.

In another large series of 649 patients with chronic leukemia (both lymphocytic and granulocytic) reported by Feinleib\textsuperscript{1} the median duration of survival after diagnosis was 11.65 months.

Lawrence\textsuperscript{4} in a study of 100 patients with chronic lymphocytic leukemia reported a mean survival of 4.5 years.

In analyzing the laboratory data of this study the hemoglobin values will be considered first. According to Wasi\textsuperscript{12}, before the availability of radioisotope techniques it was generally accepted that replacement of erythroblasts by leukemic cells was the mechanism by which anemia developed. However, since the bone marrow was rarely biopsied, this opinion was based almost entirely on the histopathology of the marrow at autopsy; patients early in the natural history of their disease were not studied. In Wasi's\textsuperscript{12} study all the patients with a normal hemoglobin level had a normal amount of erythroblastic
tissue and the degree of anemia was roughly correlated with the decrease in erythroblastic tissue.

There is also a massive replacement of the myeloid tissue as well as erythroblastic tissue. These elements are replaced by the lymphatic tissue. It therefore seems reasonable that the degree of anemia would be proportional to the decrease in erythroblastic tissue and hence, to the increase in lymphatic tissue. It might be expected that a patient's prognosis could then be estimated on the basis of the hemoglobin value. This is assuming of course, that the replacement of the bone marrow with lymphatic tissue carries a poor prognosis.

The results of this study seem to give support for the above reasoning. On examining figure 3 it is observed that most of the values are clustered in the upper left triangle of the graph. Of the 32 values under 12 Gm.% 22, or 69%, died before reaching the mean survival of 3.31 years. Of the 32 values above 12 Gm. % 18, or 56%, lived longer than 3.31 years.

The peripheral lymphocyte count may also be a measure of the amount of lymphatic tissue in the marrow and hence, an indication of the progression and duration of the disease in a specific patient. The expected result might be that a high lymphocyte count indicates a poor prognosis.
This was again shown to have some correlation. When figure 4 is studied, it is observed that most of the values are clustered in the upper right triangle. Of the 29 values greater than 50,000 white blood cells per cu. mm. 16, or 55%, died before surviving 3.31 years. Ten, or 34%, of the values less than 50,000 died before surviving 3.31 years.

The percentage of reticulocytes was also included in this study because of its direct correlation with erythropoietic activity. An increase in the number of reticulocytes in the peripheral blood is indicative of erythropoietic hyperactivity while a decreased number or a normal or only slightly increased number in the presence of anemia is indicative of hypoactivity or inadequate regenerative response. Therefore, if the marrow is replaced by lymphatic tissue, this may be reflected in the peripheral blood by a decrease in reticulocytes. It is the purpose of this study to see if this would indicate a poor prognosis.

The values in figure 5 are clustered in the lower left triangle. There are 14 values that fall outside of the normal range of 0.5-1.5%. Only five, or 36%, lived longer than the mean survival time. Ten of the 24 values, or 42%, lived longer than 3.31 years.
Thrombocytopenia is not prominent throughout the greater part of the course in most cases of chronic lymphocytic leukemia, although it commonly develops terminally, usually as part of an aplastic syndrome of marrow failure with accompanying failure of red cell production. If marrow failure is indicative of a poor prognosis, then it is possible that a reduction in the number of platelets in the peripheral blood may also be associated with a poor prognosis.

The majority of values in figure 6 are clustered in the lower left triangle. Sixteen values fall outside of the normal range of 150,000-600,000 per cu. mm. Only two, or 12%, of these patients lived longer than 3.31 years. Twenty-one, or 44%, of the values within the normal range lived longer than the mean survival period. Because of the method used in reporting platelet determinations (decreased, normal, increased, etc.), it was not possible to arrive at an actual mean platelet value.

Since the degree of cellularity in the bone marrow is usually proportional to the degree of lymphatic infiltration in chronic lymphocytic leukemia, this may give some indication of the patient's prognosis. It was also not possible to arrive at a mean cellularity value because of the method used in reporting the
findings. None of the patients were found to have hypocellular marrows. Of the seven patients with normal marrow cellularity four, or 52%, survived longer than the mean 3.31 years. A better correlation was observed in the group of 19 patients with markedly hypercellular bone marrows at the time of diagnosis. Seventeen, or 90%, of these patients died before reaching the mean survival interval of 3.31 years.

The serum proteins in chronic lymphocytic leukemia may show more striking variations from normal than are seen in other forms of leukemia. This is to be expected in view of the close relationship of lymphocytes to plasma cells and other cellular components of the lymphoid and reticulo-endothelial system, with their probable functions in elaborating antibodies and globulins. Nevertheless, no consistent abnormalities of electrophoretic protein patterns occur, and the majority of patients with clinically mild chronic lymphocytic leukemia show no differences from normal. At later stages of the disease a marked increase in gamma globulins may be found, or there may be a conspicuous hypogammaglobulinemia.\(^2\)

According to Klein and Block\(^3\) plasma cells produce serum antibodies. Although there is still no uniformity of opinion concerning the function of plasma cells, they...
believe there can be little doubt that plasma cell proliferation is usually associated with elevated plasma globulin levels. If this is true, then there may be some correlation between the number of plasma cells in the bone marrow at the time of diagnosis and the eventual prognosis of the patient.

Only 30 patients in this series had their bone marrow plasma cell findings recorded. Of this number only six were reported as being decreased. Five of these, or 83%, died before the mean survival period of 3.31 years. Only four patients had bone marrows that showed an increase in plasma cells. Three of these, or 75%, also died before the mean survival period of 3.31 years. The remaining 20 patients had a normal number of plasma cells in their marrows.

Efforts to correlate the patient's prognosis with the percentage of cells in the lymphocytic series in the bone marrow was also attempted. It seems reasonable to assume that the greater the percentage of cells in the lymphocytic series, the greater the progression of the disease and hence, the poorer the prognosis.

Twenty-eight patients had more than 70% of their bone marrow replaced with cells in the lymphocytic series. Sixteen, or 57%, of these died before reaching the mean
survival period. Eighteen, or 60%, of the patients with less than 70% of their marrow replaced also died before reaching the mean survival period.

It is interesting to compare these blood findings with a report by Marlow of a patient who lived 29 years with chronic lymphocytic leukemia. His initial hemoglobin was 75% (about 10 Gm.%), white blood cell count was 48,800 and the initial differential showed 86% lymphocytes.

SUMMARY

A series of 64 patients with chronic lymphocytic leukemia was studied to determine if their prognosis could be predicted by the peripheral blood smear and bone marrow findings at the time of diagnosis.

The sex ratio was about 2:1 with the males predominating.

The mean age at the time of diagnosis was 67.0 years with a range of from 38 years to 87 years.

Presently, 20 of the patients are living and 44 have died. The deceased patients lived an average of 2.76 years after diagnosis. The living patients have survived for a mean period of 4.51 years since being diagnosed. All patients in this series, as a group, have a mean survival value of 3.31 years. It is this
figure that is used to compare with the various blood findings.

Of the 32 patients with hemoglobins below 12 Gm.% 69% survived less than 3.31 years. Fifty-six per cent of the patients whose hemoglobin was above 12 Gm.% died in the same time interval.

Of the 29 patients who had white blood cell counts higher than 50,000 per cu. mm. 55% lived less than the mean survival time. Those with counts below 50,000 per cu. mm. had 29% that did not live 3.31 years.

The mean value for the percentage of cells of the lymphocytic series in the differential was 81%.

The normal reticulocyte response was considered to be 0.5-1.5%. Only 36% of the patients with values outside of this range survived more than 3.31 years. Forty-two per cent of the values within the normal range lived longer than the mean survival period.

Sixteen patients had platelet counts outside the normal range of 150,000-600,000 per cu. mm. Twelve per cent of these survived longer than 3.31 years. Only 44% of the patients who had normal platelet counts survived longer than this period.

The cellularity of the bone marrow was studied in this series of patients. Of the seven patients with normal cellularity 52% survived longer than the mean
period. Ninety per cent of the patients with markedly hypercellular marrows failed to survive 3.31 years.

Five out of six patients with a decreased number of plasma cells in their marrow died before 3.31 years. Also, three out of four patients with an increase in marrow plasma cells failed to survive the same period of time.

Seventy per cent replacement of the bone marrow by cells of the lymphocytic series was used as a figure for comparison. Fifty-seven per cent of patients with greater marrow replacement died before 3.31 years. Of the patients with less than this amount of replacement 60% died before the mean survival period was reached.

CONCLUSION

The following conclusions are based on this study of 54 patients with chronic lymphocytic leukemia at or near the time of diagnosis.

1. The mean age at the time of diagnosis is substantially higher than that reported by other investigators. This may be due to the source of information. The average age of the patient treated at the University of Nebraska College of Medicine is probably higher than the age of patients in other series.
2. The mean duration of survival compares favorably with values given by other authors.

3. Within broad limits, a higher hemoglobin indicates a better prognosis.

4. The white blood cell count shows fair correlation in being inversely proportional to the length of survival.

5. Reticulocyte counts outside the normal range have a poor prognosis.

6. Platelet counts outside the normal range indicate a poor prognosis.

7. A markedly hypercellular bone marrow indicates a poor prognosis.

8. An increased or decreased number of plasma cells in the bone marrow carries a poor prognosis.

9. The percentage of cells in the lymphocytic series gives no good indication of the eventual prognosis.

All of the conclusions in this series are based upon the assumption that all of the patients are deceased. This was necessary in order to obtain a series large enough to be of some significance. Therefore, after all of the patients are actually deceased the conclusions may be markedly altered.
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