The Influence of Chemotherapy on Survival in Acute Leukemia

III. A Comparison of Patients Treated During 1958-1964 with Those Treated in Two Sequentially Preceding Periods

By A. Mangalik, D. R. Boggs, M. M. Wintrobe and G. E. Cartwright

Before the introduction of adrenal glucocorticosteroid (steroid) and folic acid antagonist (FAA) therapy in the late 1940's, no therapy was capable of altering the clinical course of acute leukemia significantly and consistently. Analysis of a series of patients treated in this clinic during the years 1947-1954 (series I), which included many patients treated with FAA and steroids, failed to reveal a significantly longer survival than that reported in pre-chemotherapy series. However, a second series of patients treated during the years 1954-1957 (series II), in which some patients were treated with 6-mercaptopurine (6-MP) as well as FAA and steroids, survived for a significantly longer period of time than did the patients in series I. The improved survival of series II as compared to series I was demonstrable in lymphoblastic leukemia only. No statistically significant difference in survival of patients with myeloblastic leukemia was demonstrated between these series.

This report is concerned with analysis of a third series of patients treated during the years 1958-1964.

Materials and Methods

All patients with acute leukemia who were examined in the hematology clinic at the University of Utah College of Medicine between 1947 and July 1, 1964, are included in this report. Data on living patients were collected until January 1, 1965. Survival was calculated from the date of diagnosis until death and expressed to the nearest whole month. Twelve patients who were lost to follow-up were considered dead on the last date that they were known to be alive. Twelve patients who were alive on January 1, 1965, were considered to be dead on that date in calculating survival figures. Untreated patients were excluded from the original reports on series I and series II but are included for those periods in this report; consequently, a larger number of patients are listed in series I and II in this report as compared to the originally reported data.

Diagnostic criteria have been reported. Classification of cases as myeloblastic or lymphoblastic was based solely on the morphologic appearance of the immature cells.

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accuracy with which this classification can be reproduced has been analyzed. As defined previously, the classification of myeloblastic leukemia includes patients in whom the predominant cell had certain monocytic characteristics or was a promyelocyte.

Since, in a study of our first 322 patients, factors other than chemotherapy were found to influence survival, the comparability of the three series was examined. In that study, a relatively poor prognosis was demonstrated in patients with myeloblastic leukemia, with more than 100,000 blasts/mm$^3$ of blood, with sternal tenderness and with serious hemorrhage at diagnosis as compared to that of patients without these findings. There was no significant difference in the frequency of these factors in series I, II or III. The median duration of time between the onset of symptoms and diagnosis (4 weeks in lymphoblastic leukemia, 6 weeks in myeloblastic leukemia) did not differ in the three series. The median duration of time elapsing between the patient’s first visit to a physician with symptoms of acute leukemia and our first examination of the patient was less than 2 weeks.

Adults and children are combined since there was no significant difference in their survival in any series. Statistical comparison of survival of one series with that of another was by Mantel’s chi square method.

The number of patients, the proportions of children and adults, and the frequency of myeloblastic and lymphoblastic leukemia in each of the three series are listed in Table 1. The frequency with which steroids, 6-MP and FAA were used in each series is listed in Table 2.

### RESULTS

The median survival of patients with lymphoblastic leukemia was 3.6 months in series I, 7.9 months in series II, and 12.3 months in series III (fig. 1A). The proportion of patients living at least 1 year was significantly greater in each succeeding series as compared with the preceding one (p = < 0.05).

Whenever possible, patients with lymphoblastic leukemia in series III were treated in the following manner. As soon as the diagnosis was made, treatment with 40 mg. of prednisone per day was begun and continued for 6 weeks. After 6 weeks of prednisone therapy the blood and physical examination was normal in two-thirds of the patients and over 90 per cent were significantly improved. Six-MP was then begun at 2.5 mg./Kg./day and continued, with adjustments in dose with development of toxicity until the patient relapsed. This sequence was then repeated with prednisone and amethopterin. Less than one-half of the patients respond to a second course of prednisone, so amethopterin was used frequently in the role of a remission inducer as well as a remission maintainer. Forty-four per cent of patients in series III enjoyed a second remission. When relapse from a second remission was evident, a third course of prednisone was given, providing the patient had responded to the second course. A few patients will respond to prednisone on three occasions. If the patient did not respond to the second course of prednisone, then a variety of other drugs were tried, including cyclophosphamide, vinblastine sulfate, very large doses of steroids, and second courses of 6-MP and FAA. Such therapeutic trials were usually unsuccessful. In recent months, remissions have been induced in 1 of 3 patients given vincristine. Overall, 10 per cent of patients in series III achieved a third remission.

Forty-one patients were begun on the above regime of “sequential” chemotherapy. The median survival of this selected series was 15.3 months (fig. 1A).
Table 1.—*The Population of Patients with Acute Leukemia*

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>Age Groups (years)</th>
<th>I 1947-1954</th>
<th>II 1954-1957</th>
<th>III 1958-1964</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoblastic</td>
<td>15 or older</td>
<td>10</td>
<td>15</td>
<td>17</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>under 15</td>
<td>54</td>
<td>61</td>
<td>53</td>
<td>168</td>
</tr>
<tr>
<td>Myeloblastic</td>
<td>15 or older</td>
<td>44</td>
<td>58</td>
<td>74</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>under 15</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 2.—*The Frequency with which Steroids, 6-Mercaptopurine (6-MP) and Folic Acid Antagonists (FAA) Were Used in Three Sequential Periods in Patients with Lymphoblastic and Myeloblastic Leukemia*

<table>
<thead>
<tr>
<th>Drugs Employed</th>
<th>Lymphoblastic Series†</th>
<th>Myeloblastic Series†</th>
<th>Total number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids, 6-MP and FAA*</td>
<td>I 1</td>
<td>II 1</td>
<td>III 1</td>
</tr>
<tr>
<td>Steroids and 6-MP*</td>
<td>0 0</td>
<td>10 10</td>
<td>19 19</td>
</tr>
<tr>
<td>Steroids and FAA*</td>
<td>16 16</td>
<td>6 6</td>
<td>0 0</td>
</tr>
<tr>
<td>6-MP and FAA*</td>
<td>0 0</td>
<td>2 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Steroids</td>
<td>15 15</td>
<td>8 8</td>
<td>5 5</td>
</tr>
<tr>
<td>6-MP</td>
<td>0 0</td>
<td>1 1</td>
<td>1 1</td>
</tr>
<tr>
<td>FAA</td>
<td>13 13</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>None of these drugs</td>
<td>16 16</td>
<td>3 3</td>
<td>1 1</td>
</tr>
</tbody>
</table>

*As detailed in the text, these drugs were used sequentially, not concurrently.
†Series I was treated 1947-1954; series II was treated 1954-1957; series III was treated 1958-1964.

The longest survivor, a 23-year-old woman, was in the 64th month of her first remission when this study was concluded.

The median survival of patients with myeloblastic leukemia was 2.2 months in series I, 3.4 months in series II, and 5.1 months in series III. The proportion of patients living for at least 3 months or 6 months is significantly larger in series III than in series I (p = <.05).

Six-mercaptopurine was the preferred form of initial therapy of patients with myeloblastic leukemia. Six-mercaptopurine, 2.5 mg./Kg./day, was given for a minimum period of 8 weeks, providing neither death nor drug toxicity supervened. If significant improvement attended this therapy, 6-MP was continued until relapse was evident. When relapse occurred or if improvement did not attend 6-MP therapy, a variety of drugs were tried—without any apparent benefit. There were, in all 3 series, a total of 98 patients with myeloblastic leukemia in whom the results of therapy with 6-MP were known. Twenty-four of the 98 responded to therapy with either a remission or improvement. The median survival of patients responding to therapy was 9.5 months as compared to 3.0 months in the 74 patients who failed to respond to 6-MP therapy.
Fig. 1.—The survival of patients with lymphoblastic (A) and myeloblastic (B) leukemia. The percentage of patients living is plotted at 1-month intervals from the time of diagnosis of leukemia. In (A) the solid line with dots represents patients treated with our preferred regime of sequential chemotherapy; the solid line with circles represents patients treated 1958-1964; the broken line with dots represents patients treated 1954-1957; and the broken line with circles represents patients treated 1947-1954. In (B) the solid line with dots represents patients treated 1947-1954; the broken line with dots represents patients treated 1954-1957; and the solid line with circles represents patients treated 1958-1964.

DISCUSSION

The significant increase in survival of patients with myeloblastic leukemia in series III as compared to series I constitutes the first statistical evidence that survival of patients with myeloblastic leukemia is prolonged by chemotherapy. The difference in survival in patients in series I and III is assumed to reflect the more frequent use of 6-MP in series III. This assumption is supported by the observation that of patients with myeloblastic leukemia treated with 6-MP, those that improved with 6-MP lived longer than those that did
not. However, the possible influence upon survival of such variables as subtle differences in patient populations or of therapy for complications such as infection and hemorrhage cannot be assessed in a sequential study. Consequently, although the difference in survival of patients in series I and III is significant statistically, some may question whether or not 6-MP deserves credit for the improved survival. However, the occasional association of 6-MP therapy with symptom-free remissions of a year or more in duration, the slight but significant increase in median survival in a group of patients treated with 6-MP as compared to those not treated with 6-MP, and the natural desire of most patients and physicians to avoid a nihilistic therapeutic attitude lead us to the opinion that a trial of 6-MP therapy is worthwhile in patients with myeloblastic leukemia.

The low rate of significant hematologic improvement in patients with myeloblastic leukemia treated with 6-NIP (24 per cent in this series) and the still distressingly short median survival (5 months) makes this disease the most malignant of all the neoplastic diseases of the blood-forming organs.

Recent reports suggest that large intermittent doses of amethopterin and a new drug, methyl glyoxal-bis-guanyl hydrazone (Methyl GAG) may be of benefit in myeloblastic leukemia. Levin and co-workers observed complete remission in 25 per cent of 68 patients with myeloblastic leukemia treated with methyl GAG and a 45 per cent remission rate in 31 of these patients treated with what they considered to be an optimal dosage schedule. However, these authors concluded that “enthusiasm for this agent’s antileukemic powers is tempered by the frequent, severe, or disabling toxic effects associated with its administration.” Nonetheless, such reports constitute the first evidence that drugs other than 6-MP will induce improvement in a greater percentage of patients than will a placebo.

The median survival of patients with lymphoblastic leukemia increased from 4 to 8 to 12 months in the three time periods which were studied. Steroids, FAA and 6-MP are all of distinct benefit in lymphoblastic leukemia and the proportion of patients treated with all three of these drugs increased from 6 per cent to 61 per cent to 63 per cent in the three series. The proportion of patients treated with steroids and either FAA or 6-MP increased from 31 per cent to 81 per cent to 90 per cent in the three series. The duration of survival has been shown to be directly proportional to the duration of therapy with effective agents. Thus, increased usage of effective chemotherapy, accompanied presumably by more efficient usage of each drug as the physician becomes more familiar with its effects, would appear to be sufficient explanation for the increased survival.

The median survival of patients with lymphoblastic leukemia in series III is similar to that reported recently from a number of other clinics. However, Meighan from studies of patients in Saskatchewan and in Oregon, and Bjelke from studies in Norway, have suggested that a median survival of 12 months or more is an unrealistic figure. These authors suggest that series from hematology clinics are highly selected in terms of good sur-
vivors, although Meighan proposes a second alternative—namely, that patients in hematology clinics receive better care than do a general population of patients with leukemia. Differences between our series and those of Bjelke and Meighan warrant examination.

Bjelke analyzed all patients in Norway under age 20 reported as having acute leukemia during 1953-1958. Of the 237 patients, those diagnosed in 1953-1955 lived a median of 2 months and those diagnosed in 1956-1958 lived a median of 3 months. Meighan analyzed two “unselected” series. In Saskatchewan, between 1948 and 1960, 105 patients less than 15 years of age were discovered to have acute leukemia. In his 1948 to 1954 subgroup the median survival was 2 months, and in the 1955 to 1960 subgroup the median survival was 4 months. A second series of 255 children with acute leukemia was collected by Meighan from death certificates in Oregon from 1950 to 1961. The median survival increased from 2 to 6 months between the 1950-1955 and 1956-1961 time periods. Our series II patients correspond roughly in time to the second time period in Bjelke and Meighan’s studies. The median survival of all patients (lymphoblastic and myeloblastic combined) in series II under age 20 was 7 months; under age 15 it was 8 months. Is the difference in survival between our series and the “unselected” series of Bjelke and Meighan explainable primarily on the basis of patient selection? A completely definitive answer cannot be given but a number of factors suggest a negative one.

Median survival of our series, including all patients examined, has increased in each of the 3 time periods studied. There is no reason to suppose that the type of patient referred to us has changed during these periods. Obviously, a few patients who would have been referred to us die before this can be accomplished, and perhaps as many as 1 per cent of all patients in whom leukemia is diagnosed are diagnosed only at autopsy. However, more than one-half of our patients were examined by us within 2 weeks of the time they first consulted a physician for symptoms of leukemia. The suggestion that hematology clinic series are prejudiced by the referral of patients who are already doing well was examined. The median survival of patients with lymphoblastic leukemia in series III referred within 2 weeks of consulting a physician was 2 months longer than that of patients referred after a longer interval. One might suggest that patients who are not doing well are more likely to be referred to a hematology clinic and thus adversely prejudice survival figures.

Only one-fourth of the patients in Bjelke’s series received steroids and FAA or 6-MP, whereas more than three-fourths of our patients in series II received such therapy. This difference alone could explain the difference in survival. Details of therapy were not included in Meighan’s analyses.

In the original report of our series II patients, untreated patients were excluded from analysis of survival. Meighan suggested that if these patients had not been excluded, the median survival of our cases would not have exceeded 4 months. In the present analysis we have excluded no patients.
Nevertheless, the median survival for children in series II was 8 months, which is considerably more than that in Meighan's series in the corresponding time period.

The longest median survival reported in the literature is 17 months for Zuelzer's selected series of patients with lymphoblastic leukemia given "cyclic" chemotherapy. In this group of patients remission was induced with concurrent 6-MP and steroid administration and then 6-MP and FAA were given for alternate 3-month periods for the duration of the remission. No statistically significant differences are demonstrable between the curve of survival for that series and for our selected series of patients treated with "sequential" chemotherapy (fig. 1A).

The use of various drugs in combination, although associated with more toxic effects than drugs used singly, if used as initial therapy for lymphoblastic leukemia leads to a higher rate of complete remission than that observed herein with steroids alone. Since a cure for acute leukemia has not yet been discovered, a major consideration in the treatment of these patients involves the effect of therapy upon well-being in addition to duration of survival. Consequently, the possibility of outpatient management in contrast to hospitalization, the need for frequent outpatient visits as compared with more infrequent ones, the requirements entailed in parenteral therapy as compared with oral, the incidence of toxic effects with different forms of therapy, and the financial drain upon the patient's family are all factors which cannot be overlooked. For these reasons we are at present continuing to use steroids alone as initial therapy for patients with lymphoblastic leukemia. Our reasons for doing so are three-fold. First, patients who improve but do not attain complete remission status with steroids usually go on to complete remission when 6-MP is introduced as maintenance therapy. Second, the absence of myelotoxicity associated with steroid therapy reduces the need for hospitalization and frequent clinic visits. Third, there is no definitive evidence to suggest that other forms of therapy lead to a significantly longer survival than does the regime used herein. It is possible that refinements in the manner in which currently available therapy is employed will lead to a significantly longer median survival than that reported herein. However, the essential ingredients of all regimes which have been reported to prolong significantly the life of patients with lymphoblastic leukemia would appear to be induction of remission with steroids, with or without concurrent administration of other drugs, plus continuous antimetabolite maintenance therapy during remission.

**SUMMARY**

Three-hundred and ninety-nine patients with acute leukemia examined during the period 1947-1964 were divided into three sequential series and their survival, from diagnosis to death, was compared.

A statistically significant increase in duration of survival for myeloblastic leukemia from a median of 2 to 5 months occurred between series I and series III. This is the first convincing evidence that 6-mercaptopurine therapy influences survival in myeloblastic leukemia.
A steady increase in median survival of patients with lymphoblastic leukemia from 4 to 8 to 12 months was found in the three series. The results of analysis of these series are compared to other reported series. The hypothesis—that the longer survivals reported for patients treated in hematology clinics compared to that of patients selected from population areas reflects patient selection—was examined and appeared unlikely.

SUMMARIO IN INTERLINGUA

Tres centos novanta-novem patientes con leucemia acute examine durante le periodo ab 1947 ad 1964 esseva dividite in tres series sequential, e lor periodos de superviventia ab le tempore del diagnose usque al morte esseva comparate.

Un augmento de signification statistic occurreva in le duration del superviventia de patientes con leucemia myeloblastic ab un valor median de 2 menses ad un valor median de 5 menses inter serie I e serie III. Isto es le prime convincente evidentia que therapia a 6-mercaptopurina exerce un influentia super le longevitate in leucemia myeloblastic.

Un continue augmento in le superviventia median de patientes con leucemia lymphoblastic ab 4 ad 8 ad 12 menses esseva trovate in le tres series. Le resultatos del analyse de iste series es comparate con altere series reportate in le litteratura. Esseva examine e reguardate como pauco probable le hypothese que le prolongate superviventias reportate pro patientes tractate in clinicas hematologic in comparation con illo de patientes seligite ab le population general es un effecto del selection del patientes e non del therapia.

REFERENCES


The Influence of Chemotherapy on Survival in Acute Leukemia: III. A Comparison of Patients Treated During 1958-1964 with Those Treated in Two Sequentially Preceding Periods

A. MANGALIK, D. R. BOGGS, M. M. WINTROBE and G. E. CARTWRIGHT