Comparison of Daily Versus Intermittent Chlorambucil and Prednisone Therapy in the Treatment of Patients With Chronic Lymphocytic Leukemia

By Arthur Sawitsky, Kanti R. Rai, Oliver Glidewell, Richard T. Silver, and participating members of CALGB (Cancer and Leukemia Group B)

Ninety-six patients with stage III and stage IV chronic lymphocytic leukemia (CLL) were randomized into one of three treatment schedules. Prednisone was common to all three schedules and was given daily in an initial dosage of 0.8 mg/kg for the first 14 days, with successive halving of the daily dose on days 15 and 29 for a total 6-wk course. Prednisone was then given once a month at 0.8 mg/kg once a day for each of 7 consecutive days. Schedule I was prednisone plus chlorambucil (CLB) given as a once-a-month dose of 0.4–0.8 mg/kg; schedule II was both drugs, but the CLB was given as a daily dose of 0.08 mg/kg; schedule III was prednisone alone. Complete and partial remission (CR + PR) was 47% for schedule I, 38% for schedule II, and 11% for schedule III. Patients who responded (CR + PR) in each of the treatment schedules survived longer than the nonresponders. Complete remission was obtained in both CLB treatment schedules, but not with the prednisone alone regimen. Although overall survival was best in the intermittent CLB arm, there was no significant difference in survival time between the three treatment schedules. Toxicity was minimal in all three regimens. Augmentation of the intermittent monthly CLB, even to 1.5 and 2.0 mg/kg, was tolerated without undue marrow toxicity. About 22% of these patients either had diabetes mellitus at the time of entry on the study or manifested hyperglycemia during the course of treatment and observation.

OBJECTIVE AND RELIABLE ASSESSMENT of the effectiveness of treatment schedules proposed for chronic lymphocytic leukemia (CLL) has been nearly impossible in the past. This failure can be ascribed primarily to the following reasons. Until recently the disease has been divided into two broad categories: asymptomatic and active.1 The definition of “active” disease ranged from progressing lymphadenopathy, unexplained fever, or weight loss to recurrent infections or thrombocytopenia. Active disease was considered an indication for treatment, and the results of treatment were assessed in a manner that assumed that all patients with active disease had a very similar extent of disease. The latter assumption was recently proved to be invalid, as demonstrated by a clinical staging of CLL in which stage II patients (who had evidence of active disease) had a median survival of 6 yr, whereas patients in stages III
and IV (also considered as active disease) had a median survival of 1.5 yr. It is evident, therefore, that in the assessment of the effectiveness of any therapy in CLL the patients under study must belong to a reasonably homogeneous population, with a similar extent of active disease and a similar life expectancy based on data on the natural history of CLL. The second reason for past unreliability in the assessment of new therapy in CLL has been the lack of adequate controls in the study. Even a recent therapeutic trial of two drugs in CLL relied on historical control data from studies done 12-15 yr previously. Historical controls, particularly when further complicated by a nonhomogeneous study population, cannot be considered to be reliable controls.

Studies in vivo of the rate of lymphocyte proliferation in CLL utilizing tritiated thymidine have confirmed the concept of Dameshek that CLL is characterized by the accumulation of long-lived, slowly proliferating lymphocytes. Based upon these observations, chlorambucil (CLB) therapy administered intermittently in single large doses has a theoretical advantage over the conventional low-dose daily schedule in that it allows time between doses for the recovery of normal elements of the bone marrow, long before the regeneration of the more slowly proliferating leukemic lymphocytes. Initial studies have demonstrated that such clinical trials are not only justifiable, but also feasible.

The Cancer and Leukemia Group B (CALGB) undertook a therapeutic trial in a clearly defined group of patients with CLL to examine on a prospective basis whether high-dose intermittent CLB therapy is superior to the conventional schedule of low-dose, daily CLB. Late-stage (stages III and IV) CLL patients were entered in this study because (1) the status of therapy for these patients is the least satisfactory at the present time, and improvement is urgently called for, and (2) the median life expectancy of these patients is very short; therefore, it was likely that any difference in the therapeutic efficacy between the two methods of treatment would emerge promptly.

Because all the patients had either anemia and/or thrombocytopenia, it was considered necessary that all patients be given prednisone. In addition, a third experimental arm was provided wherein prednisone was given without CLB.

**MATERIALS AND METHODS**

**Criteria for Diagnosis**

The essential criteria for the diagnosis of CLL were (1) a sustained and absolute lymphocytosis in the peripheral blood of 15,000 cells/cu mm or greater, not attributable to a cause other than leukemia, and (2) a hypercellular bone marrow, of which 50%, or more of the nucleated cells were lymphocytes. Splenomegaly, hepatomegaly, or lymphadenopathy, although common, were not required for the diagnosis of CLL.

**Criteria for Patient Selection**

Patients admitted to this study had an unequivocal diagnosis of CLL, plus anemia and/or thrombocytopenia not attributable to prior drug or radiation effects nor to causes other than CLL. Anemia was defined as a hemoglobin of 12.0 g/dl or less and/or a hematocrit equal to or less than 36% in the male, and 11.0 g/dl or less and/or a hematocrit equal to or less than 33% in the female. Thrombocytopenia was defined as 100,000 or fewer platelets/cu mm.

Prior treatment did not exclude a patient from entering the study provided that residual hematologic toxicity did not explain anemia or thrombocytopenia. The patient could not have received antileukemia therapy for at least the preceding 3 wk. Included were 24 patients who had received...
prior treatment. About half of these 24 patients had had CLB or cyclophosphamide in the past, almost 60%, had had a variable exposure to steroids, and about 45% had received some x-irradiation therapy. There was no significant difference in the type of prior treatment given patients and their distribution by randomization into the three treatment groups. Patients previously treated for long periods of time with CLB and prednisone and considered refractory were not entered in the study.

Adequate renal function and a blood urea nitrogen (BUN) of less than 25 mg/dl were required.

Study Parameters

All patients entering the study had a complete clinical appraisal and were seen at least weekly for the first 4-6 wk. A complete blood count was done and measurements of weight, lymph node, and organ size were made. An initial bone marrow aspirate and biopsy were obtained as well as urinalysis and blood chemistries, including total protein and albumin, BUN, uric acid, blood sugar, alkaline phosphatase, bilirubin, and transaminase. Direct antiglobulin test and a test for serum anti-red cell antibodies were made. A chest x-ray was obtained but bone and organ isotope scans were optional.

Patients with stable disease were seen at least once a month. Although bone marrow examination was asked for at 3-mo intervals, this requirement was not honored consistently.

Mechanics of Study

The patients were randomized to one of three treatment schedules:

Schedule I—intermittent CLB and prednisone. The patient received CLB, 0.4 mg/kg, in one dose given on day 1, day 29, and every 28 days thereafter, depending upon bone marrow function. In addition, the patient received prednisone, 0.8 mg/kg/day, in three divided doses orally for 2 wk followed by 0.4 mg/kg/day for 2 wk, and then 0.2 mg/kg/day for 2 wk. Prednisone was then stopped abruptly. Beginning with the third dose of CLB on day 57 and with each successive dose of CLB, prednisone was given at a dose of 0.5 mg/kg/day in three divided doses orally for only 7 days.

Schedule II—daily oral CLB and prednisone. CLB, 0.08 mg/kg, was given by mouth in one daily dose continuously, with prednisone given exactly as described above for schedule I.

Schedule III—prednisone alone. These patients received prednisone alone exactly as described above for schedule I.

Drug dosage modification. Drug dosage was reduced in accordance with the known toxicity of the two agents. Where there was objective evidence of inadequate response without toxicity, patients on schedule I had their dose of CLB augmented by increments of 0.2 mg/kg every 28 days. An increased dosage was given to 14 of 38 such patients. The dosage of 9 patients averaged 0.8 mg/kg and 5 others received 1.0-1.2 mg/kg. In 24 patients no change from the initial dosage was recorded. Patients on schedule II had their dose of CLB augmented in increments of 0.02 mg/kg/day; 8 patients were given an increased dosage averaging 0.10 mg/kg/day. The largest recorded daily dosage was 0.16 mg/kg. The administered daily dose was decreased to 0.04 mg/kg in 9 patients, and 22 patients received the initial dosage throughout their treatment period. There was no significant difference noted in augmentation or decrease in dosage needed between patients with prior treatment and those not previously treated. In general, more patients on daily CLB had their dose reduced (9 of 39) than those on the intermittent schedule (3 of 38). There was no provision made for augmentation of the prednisone. One year after activation of the study the initial CLB dose given to all new entries on schedule I was increased from 0.4 to 0.6 mg/kg. In only 3 patients was the dose lowered to 0.4 mg/kg.

The transfusion of blood and platelets and treatment with antibiotics, allopurinol, acetazolamide, phenothiazine, heparin, and other drugs were permitted according to clinical indications.

Criteria for Response and Relapse

A complete remission (CR) was defined as complete disappearance of all objective and subjective evidence of disease. The peripheral blood had to return to a normal level and the absolute number of lymphocytes to below 3000/cu mm. Bone marrow biopsy and aspirate had to show a normal differential pattern and there had to be less than 30% lymphocytes in the bone marrow.
A partial remission (PR) was defined as a reduction of all symptomatic evidence of disease to the asymptomatic state and improvement in measurable variables to the following degrees. The hemoglobin had to be maintained above 12 g/dl, the platelet count above 100,000/cu mm, and the blood lymphocyte count below 15,000/cu mm. Circulating blood neutrophils had to rise above 2000/cu mm. If the spleen or lymph nodes were originally enlarged, a reduction in size of at least 50% was required.

Clinical improvement was defined as a reduction in symptomatic evidence of disease to mild or no symptoms with an increase in performance status, a decrease in peripheral blood lymphocytes to 15,000/cu mm or less, and a reduction in lymph node and spleen size if initially enlarged.

No response was defined as stable disease or improvement less than the above responses. These patients were adjudged treatment failures for purposes of the study.

Progressive disease was determined to be present when at least one of the following occurred: worsening of anemia and/or thrombocytopenia from initial status over a period of 28 days; an increase in the peripheral absolute lymphocyte count and an increase in bone marrow infiltration despite therapy over a period of 8 wk; or enlarging lymph nodes, enlarging liver, or enlarging spleen over a 3-4-wk period. The study was considered to have failed and was terminated for a patient when any of the following conditions occurred: no evident benefit from the therapy schedules without progression of the disease after a 4-mo study period; the appearance of localized disease that required radiation therapy for control; relapsing disease that did not respond favorably to increased drug dose modification; or drug toxicity that precluded further drug usage.

Criteria of Toxicity

Care was exercised to distinguish disease-related signs and symptoms from drug-related side effects and drug dosage was adjusted accordingly. Toxicity when present was graded in severity on a scale of 1-4. Mild toxicity (grade 1) included absolute neutrophils less than 2000/cu mm, platelets less than 75,000/cu mm, hemoglobin less than 10 g/dl, no overt infection; only nausea and gastrointestinal disturbance, and mild euphoria. Severe toxicity (grade 3) was rated when the neutrophils were less than 1000/cu mm, platelets less than 50,000/cu mm, hemoglobin less than 8 g/dl, severe diarrhea, nausea, and abdominal discomfort, pneumonia and ecchymosis, and evidence of steroid-induced psychosis. Grade 2 toxicity was rated when any of the parameters were in between grades 1 and 3, and grade 4 toxicity was the status when grade 3 progressed to life-threatening proportions.

RESULTS

A total of 103 patients drawn from 21 cooperating institutions were randomized to one of the three treatment schedules. The accrual of patients in this study began in August 1971 and was closed in December 1974, and all patients on and off study were analyzed according to their status as of February 1, 1977. Ninety-six patients were evaluable for analysis (Table I). The characteristics of the patient population in each of the three randomization schedules were very similar, as can be seen in Table 2. At the time of an interim analysis after 2 yr of study, it was noted that the patients on schedule III (prednisone alone) had the most rapid failure rate (75% failure within 7 mo) with the lowest

<table>
<thead>
<tr>
<th>Treatment Schedule</th>
<th>No. of Patients Entered</th>
<th>Disqualified*</th>
<th>No. of Patients Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Int. CLB + prednisone</td>
<td>38</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>II. Daily CLB + prednisone</td>
<td>42</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>III. Prednisone alone</td>
<td>23</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>103</td>
<td>7</td>
<td>96</td>
</tr>
</tbody>
</table>

*Inadequate records, 1; protocol violations, 1; ineligible, 2; early loss, 3.
Table 2. Comparability of Patient Groups

<table>
<thead>
<tr>
<th>Trait</th>
<th>Int. CLB*</th>
<th>Daily CLB*</th>
<th>Pred. Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>66</td>
<td>62</td>
<td>68</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>63</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Dx to Protoc. &lt; 1 yr (%)</td>
<td>63</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Previously treated (%)</td>
<td>24</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Stage IV (%)</td>
<td>41</td>
<td>59</td>
<td>32</td>
</tr>
<tr>
<td>Marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean erythroid (%)</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Mean granulocytic (%)</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Mean lymphocytic (%)</td>
<td>87</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Dec. megakaryocytes (%)</td>
<td>59</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Packed cellularity (%)</td>
<td>50</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean hemoglobin (g/dl)</td>
<td>10.4</td>
<td>9.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Median platelets (× 10^3/cc mm)</td>
<td>142</td>
<td>95</td>
<td>139</td>
</tr>
<tr>
<td>WBC &gt; 100,000/cc mm (%)</td>
<td>26</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>Lymphs &gt; 50,000 (%)</td>
<td>50</td>
<td>61</td>
<td>79</td>
</tr>
<tr>
<td>Liver &gt; 8 cm (%)</td>
<td>13</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Spleen &gt; 8 cm (%)</td>
<td>24</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Extensive node enlarg. (%)</td>
<td>21</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Performance 2 or less (%)</td>
<td>32</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

*Plus prednisone.
†Patients spent less than 50% of their time in bed.

The data on response for all evaluable patients are detailed in Table 3. There was no CR observed in the prednisone alone schedule. Although the response rate (CR + PR) was higher in the group of patients receiving CLB intermittently (47%) as compared to the group receiving CLB daily (38%), this differ-
ence was not statistically significant \((p = 0.4)\). Response rates were, however, significantly greater in the two CLB schedules than in the prednisone alone group \((p = 0.03)\).

In the group of patients receiving intermittent CLB doses the response rate \((CR + PR)\) was 55\% for those patients who had received no prior antileukemia therapy, compared to 22\% \((CR + PR)\) response rate for those who had been previously treated. This difference, however, was found not to be statistically significant \((p = 0.28)\). There was no discernible difference noted in the two other treatment schedules between patients with and without prior treatment.

The first noted improvement in physical findings or symptoms was at 4-6 wk (median) after start of therapy in all three schedules; the first noted improvement in the peripheral blood findings was at 6 wk (median) in both CLB schedules and 8 wk in the prednisone alone schedule (Table 4). Nearly 1 yr of therapy was required to recognize bone marrow improvement in half of the patients that demonstrated such improvement. The infrequent intervals at which the marrow was examined, however, leaves uncertainty about the accuracy of these estimates.

The median time to failure or relapse (time to on-study) was 16 mo for patients receiving intermittent CLB plus prednisone, but only 7 mo for patients treated with either the daily CLB plus prednisone or the prednisone alone schedules (Fig. 1). About 74\% of patients treated by all three arms were

\[
\begin{array}{cccccc}
\text{Treatment} & \text{Bone Marrow} & \text{Peripheral Blood} & \text{Physical or Symptoms} \\
& \text{No. Eval.} & \text{Median Time (wk)} & \text{No. Eval.} & \text{Median Time (wk)} & \text{No. Eval.} & \text{Median Time (wk)} \\
\text{Int. CLB*} & 16 & 49 & 31 & 6 & 27 & 4 \\
\text{Daily CLB*} & 18 & 50 & 31 & 6 & 30 & 5 \\
\text{Pred. alone} & 3 & 27 & 14 & 8 & 12 & 6 \\
\end{array}
\]

\*Plus prednisone.
MONTHS FROM TREATMENT ONSET

FRED NORTHIT 0.8 19/36
NED'37 SOS
FRED ALONE 9/19 r(D32
SOS
FRED DRILL 0.8 25/39 NED'21 SOS

CHLORAMBUCIL, PREDNISONE IN CLL

Fig. 2. Survival time (in months), by treatment schedule, of each group of patients from entry onto protocol. Fractions: numerator, number of patients who died in each treatment group; denominator, number of patients entered in each treatment group.

treatment failures within the first 8 mo after entry on protocol, and the failure rates of all three curves during this interval (Fig. 1) were similar.

The duration of survival for patients on each of the three treatment schedules (responders as well as nonresponders) is shown in Fig. 2 and Table 3. The median duration of survival (from onset of protocol therapy) for patients receiving prednisone and intermittent CLB was 37 mo, while it was 21 mo for patients on the daily CLB schedule ($p = 0.6$). Although the duration of survival for patients treated by the prednisone alone schedule (median of 32 mo) was similar to that of the patients receiving prednisone plus intermittent CLB (Fig. 2), the former group of patients failed on the prednisone alone schedule after a median of only 7 mo (Fig. 1). These schedule III patients, now “off protocol” but still alive (9 patients), were subsequently treated with differing treatment modalities and agents. Five of these patients were placed on a schedule of intermittent CLB and prednisone (similar to schedule I), and 4 are still alive, although presently on other treatment plans.

The responders (CR + PR and improved) drawn from each of the three schedules showed a significantly longer survival than the nonresponders. Figure 3 presents these data combining patients from all three treatment schedules ($p < 0.0001$).

Patients who had previously been treated had a lower frequency of response and a shorter survival from the onset of this treatment (Table 3). However, the small number of patients prevents statistical demonstration of the significance of that observation. Those previously treated patients who did respond appeared to fare just as well as the responders who had not been previously treated. The nonresponders with prior therapy, however, had a shorter survival than those not previously treated, although again statistical significance could not be demonstrated because of the small number of patients involved.

Hematologic toxicity (Table 5), as manifested by granulocytopenia, anemia, and thrombocytopenia of more than moderate severity, was seen only in the two CLB schedules and was not statistically different in the two schedules. Although the sample size of patients with prior treatment was too small for good
comparison, there was no discernible difference in severity or incidence of toxicity between patients previously treated and those not previously treated. However, drug dosages were more often reduced in patients who had received prior treatment and were on the daily CLB schedule. Table 5 also indicates that the severity of infectious episodes in each group of patients was similar and did not limit the study. Augmentation of the single intermittent dose of CLB was tolerated even to doses of 1.5 and 2.0 mg/kg (a total single dose as high as 120 mg) without undue bone marrow toxicity. Gastrointestinal toxicity as manifested by nausea and vomiting was not severe and was only noted in those patients receiving the higher doses of intermittent CLB. However, even in these patients, this reaction was not of severity great enough to limit the dose or to limit this mode of therapy. Hyperglycemia and/or frank diabetes was documented either before entry on the study or after varying periods of treatment in 20 of 90 patients for whom data were available. This finding was observed with equal frequency in each of the three treatment schedules. Hyperosmolar acidosis complicated the treatment of one patient receiving prednisone alone who was then judged to be a treatment failure. Severe psychosis in an elderly patient followed 1 wk of prednisone therapy; this patient was deemed a treatment failure and was removed from the study.

Table 5. Toxicity According to Treatment Schedules

<table>
<thead>
<tr>
<th>Toxicity Severity With Intermittent CLB*</th>
<th>Toxicity Severity With Daily CLB*</th>
<th>Toxicity Severity With Prednisone Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1-2 3-4</td>
<td>0 1-2 3-4</td>
</tr>
<tr>
<td>Hematologic</td>
<td>19† 15 4</td>
<td>17 16 6</td>
</tr>
<tr>
<td>Bleeding</td>
<td>38 0 0</td>
<td>37 1 1</td>
</tr>
<tr>
<td>Infection</td>
<td>16 11 11</td>
<td>16 13 10</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30 6 2</td>
<td>32 3 4</td>
</tr>
<tr>
<td>Neurologic</td>
<td>36 2 0</td>
<td>37 2 0</td>
</tr>
<tr>
<td>Other</td>
<td>33 3 2</td>
<td>30 3 6</td>
</tr>
</tbody>
</table>

*Plus prednisone.
†Number of patients.
DISCUSSION

The results reported above demonstrated that in a randomized, multiinstitutional, cooperative study in which a well-defined group of patients with CLL (who had a virtually uniform short survival expectancy) were entered, (1) high-dose intermittent CLB with prednisone produced a higher incidence of response (CR + PR) than either prednisone alone or prednisone with low-dose daily CLB therapy (the difference was, however, not significant, \( p = 0.4 \)), (2) the high-dose intermittent CLB was well tolerated and produced no increase in CLB toxicity, and (3) patients on the intermittent CLB schedule remained on study longer than those on daily CLB or on prednisone alone. Although the frequency of response (CR + PR) was significantly greater for patients treated with CLB than it was for patients receiving prednisone alone, and although the occurrence of response was reflected in improved survival (Fig. 3), the overall survival by treatment schedule (Fig. 2) did not reflect the difference in response frequencies. This overall survival, however, also measured the effects of post-protocol therapies, which included cross-over treatment and the employment of differing single and combination agent plans as well as different treatment modalities.

Knopse et al., in a similar cooperative multiinstitutional study, had already demonstrated that high-dose intermittent CLB alone (without prednisone) could be used for achieving response in CLL, and that the toxicity produced by this method of CLB administration did not limit therapy. However, these investigators did not include a control arm (they used a historical control) and their patient population was a mixture of those who might be in stage I as well as in Stages II, III, and IV as defined by Rai et al. Response data in such populations, with a median life expectancy ranging from 8 to 1.5 yr, were very difficult to interpret. Han et al. had reported in 1973 that in a group of patients with different stages of CLL, daily CLB with prednisone was superior to a prednisone alone treatment regimen. Our study confirmed the superiority of schedules with CLB over prednisone alone as treatment for CLL patients with anemia and/or thrombocytopenia. However, the treatment of patients with prednisone alone did not prejudice those patients relative to their overall survival.

Although the median time on protocol was longer for the patients on the intermittent CLB schedule than on the other two schedules (Fig. 1), the overall survival as calculated from date of entry to protocol showed that there were no significant differences between patients treated by the three treatment schedules of this study. These data (Fig. 2) included all patients who were placed on study, irrespective of the status of their response to the treatment schedule or the length of time they remained on protocol. The duration of survival of patients according to response to therapy was similar for all three treatment schedules, and therefore the duration of survival for responders and nonresponders of the three schedules has been analyzed without reference to the treatment schedule. This analysis (Fig. 3) clearly demonstrated that the patients who were “responders” had a significantly higher possibility of long-term survival than the “nonresponders.”

There were 61 patients on the three treatment schedules who went off study,
and 74% of these went off within the first 8 mos. It must be appreciated that the patients entered into this study all had advanced CLL disease (stages III and IV) in which median survival was only 18 mo. The similarity in the slope of failure rate during the first 8 mo (Fig. 1) suggests that factors unrelated to treatment caused these early failures. We have so far been unable to identify these factors.

About 25% of the patients entered into this study had received prior treatment with either CLB, cyclophosphamide, prednisone, or x-ray therapy as single agents or in some combination. Analysis of the data reflected the fact that random chance alone allowed for an almost equal distribution of these modalities of prior treatment between the three treatment regimens. The data also showed that the group of prior therapy patients were not a selected group of all “survivors” or “responders,” although there were long-term prior therapy survivors in each treatment arm. Prior treatment patients did not respond (CR + PR) as well as the group with no prior treatment (Table 3), but the differences noted were not statistically significant \( p = 0.28 \). Furthermore, prior treatment did not produce more drug toxicity in our study nor did it influence total drug dosage administration to the patient.

We believe that the single positive observation that emerged from this study was that the patients who responded to therapy were the ones who eventually became the longer survivors \( p < 0.0001 \) (Fig. 3). Not all responders were on the study all through the period of survival, and several patients went off the study after having shown a CR or PR, and achieved response again to subsequently employed nonprotocol therapy. This finding emphasizes the need for treatment schedules that maximize the remission induction frequency and the completeness of response in CLL patients in stages III and IV.

This study emphasizes the complicating role of infection during the course of this disease. In all three treatment schedules there were similar frequencies of infectious episodes; about 26% of patients had severe infectious complications and 30% had infections of milder degree. No one drug treatment schedule, however, was found to be better or worse than any other. In addition, complications due to prednisone treatment, i.e., hyperosmolar acidosis, severe psychosis, and serious problems with diabetes control, also occurred in all three treatment schedules, but these affected only 10% of all patients. About 22% of all patients (20 of 90 patients evaluable) were known to be diabetic or developed significant hyperglycemia during therapy. Whether this finding reflects the age group of the patients under study or has significance related to the underlying CLL has not been determined.

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