A Study of Prednisone Therapy in Chronic Lymphocytic Leukemia

By Richard K. Shaw, Dane R. Boggs, Harold R. Silberman and Emil Frei, III

Since the original description, in 1949, of beneficial effects induced by cortisone and adrenocorticotropic hormone (ACTH) in patients with chronic lymphocytic leukemia, there have been several reports on the use of these compounds and related adrenal corticosteroids in the treatment of this disease. Although antileukemic effects have been observed, the place of corticosteroid therapy for the primary disease is poorly defined. At present the adrenal corticosteroids are generally reserved for the management of complications such as symptomatic hemolytic anemia and thrombocytopenia.

There is considerable evidence from animal studies that adrenal corticosteroids increase susceptibility to infection. In man the evidence is only suggestive. Infections are frequent complications in patients with chronic lymphocytic leukemia, and have been attributed in part to the concomitant administration of adrenal corticosteroids. It has been demonstrated that patients with chronic lymphocytic leukemia frequently have hypogammaglobulinemia, and a profound deficit in circulating antibody production. In a previous report, we have described a correlation between the failure of patients with chronic lymphocytic leukemia to produce circulating antibodies and the occurrence of bacterial infections. Since the adrenal corticosteroids are generally used in patients who have already received considerable therapy capable of depressing the bone marrow and who are near the terminal phases of their disease, it is difficult to determine retrospectively what role they play in the development of infections.

Since control of the leukemic process could result in an increased host resistance to infection, the question of whether corticosteroid therapy is harmful or beneficial would have to be answered on the basis of a clinical trial. A controlled study of prednisone therapy was, therefore, undertaken with these objectives: (1) to define the antileukemic effect of prednisone in chronic lymphocytic leukemia and (2) to determine whether prednisone affected the frequency and/or character of infections.

Materials and Methods

Twenty-four patients with chronic lymphocytic leukemia were referred to the National Cancer Institute between July, 1958 and June, 1959. All of these patients had previously participated in a study of antibody formation and, of the 24, 18 were selected for the...
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present study (table 1). There were 16 males and two females with an age range of 32 to 74 years and a median age of 58 years. The diagnosis was confirmed by examination of the peripheral blood and bone marrow. Their duration of disease, from the time of diagnosis, ranged from one to 132 months with a median of 13 months. All patients were ambulatory and could be cared for on an outpatient basis. Nine of the patients had received no prior antileukemic therapy. Only three patients had previously received adrenal corticosteroids.

The six patients who were not entered in the prednisone study were excluded for the following reasons: inability to follow, 2; active duodenal ulcer, 2; death, 1; and psychiatric problems, 1. Following completion of the antibody study, the patients were randomly assigned to two therapeutic programs; (1) prednisone for 12 weeks followed by a 12 week control period, and (2) a control period for 12 weeks followed by prednisone for 12 weeks. The 12 week periods were chosen on the basis of earlier experience which indicated that maximal antileukemic effect occurred within 12 weeks.²⁻¹

Prednisone was administered orally in three to four doses per day. The initial daily dose of prednisone, was 1 mg./Kg. This was decreased to 0.5 mg./Kg. after four weeks and to 0.25 mg. Kg. on the eighth week of therapy. At the completion of 12 weeks, prednisone was discontinued. No other antileukemic therapy was used during the treatment or control period. In the face of severe infections the dose of prednisone was increased. Antacids and potassium salts were not routinely administered.

During the study, the patients were seen at least every two weeks. At each visit, symptoms were recorded, a physical examination performed, and hemoglobin, white blood count, differential count, platelet count, and reticulocyte count were determined. Serum protein electrophoresis was performed at biweekly intervals.

Serum gamma globulin was measured by analytical paper electrophoresis, and the total serum protein was determined by the Biuret technic as previously described.²⁴ The normal range in this laboratory for gamma globulin is 1.17 Gm. per cent with a standard deviation of ± 0.20 Gm. per cent. Hypogammaglobulinemia was considered to exist when the gamma globulin was less than 0.77 Gm. per cent (two standard deviations below the normal mean).

Response to prednisone was analyzed in terms of symptoms, leukemic cells in blood and marrow, organ size and normal blood corpuscular elements. Because of the discordant white count effect (see below), previously used criteria for the degree of remission were not considered applicable.

All significant infections are included in Table 4. Minor clinical episodes such as exacerbations of chronic bronchitis without fever, upper respiratory infections and activation of chronic eczema without true cellulitis have not been tabulated. The severity of each infection was determined from the data presented in Table 4 and rated on a 1+ to 4± scale. These clinical ratings were made both by the physician in charge of the patient and by a physician who was unaware as to what antileukemic therapy the patient was receiving.

RESULTS

Nine patients were included in each of the two therapeutic programs. During the study, two patients who were receiving prednisone expired. One, case number two (table 1), died with bacterial pneumonia and bleeding duodenal ulcer after five weeks of prednisone, and the second, case number three, expired with miliary tuberculosis after 11 weeks of prednisone. It was necessary to discontinue prednisone in two other patients, because of a psychotic depression in one after five weeks and intractable herpes genitalis in the second after seven weeks. Seventeen patients completed the 12 week control period. The patient with the psychotic depression did not enter the control period. As a result of such factors, the total patient time on prednisone was 1416 days while the total patient time in the control period was 1558 days.
Table 1.—Status of Eighteen Patients at Onset of Prednisone Study

<table>
<thead>
<tr>
<th>Case No.</th>
<th>N.I.H. No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Duration from Symptoms (in months)</th>
<th>Disease</th>
<th>Prior Therapy</th>
<th>History of Infection</th>
<th>White Blood Cell Count (1,000/mm³)</th>
<th>Hemoglobin (gm. %)</th>
<th>Platelets (1,000/mm³)</th>
<th>Absolute Neutrophil Count (1,000/mm³)</th>
<th>Gamma Globulin (gm. %)</th>
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<tr>
<td>1</td>
<td>00-98-50</td>
<td>57</td>
<td>M</td>
<td>12</td>
<td>1</td>
<td>None</td>
<td>Bronchitis</td>
<td>62</td>
<td>5.0</td>
<td>18</td>
<td>1.2</td>
<td>0.44</td>
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<td>2</td>
<td>02-09-89</td>
<td>74</td>
<td>M</td>
<td>4</td>
<td>2</td>
<td>None</td>
<td>Bronchitis</td>
<td>90</td>
<td>9.0</td>
<td>218</td>
<td>5.0</td>
<td>0.22</td>
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<td>3</td>
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<td>M</td>
<td>3</td>
<td>3</td>
<td>x-ray</td>
<td>None</td>
<td>160</td>
<td>14.0</td>
<td>200</td>
<td>9.0</td>
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<td>4</td>
<td>02-29-49</td>
<td>58</td>
<td>M</td>
<td>28</td>
<td>2</td>
<td>None</td>
<td>Cellulitis</td>
<td>207</td>
<td>7.3</td>
<td>144</td>
<td>18</td>
<td>1.42</td>
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<td>00-94-05</td>
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<td>M</td>
<td>0</td>
<td>1</td>
<td>None</td>
<td>None</td>
<td>23</td>
<td>15.3</td>
<td>230</td>
<td>4.0</td>
<td>1.13</td>
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<tr>
<td>6</td>
<td>01-94-43</td>
<td>42</td>
<td>M</td>
<td>18</td>
<td>12</td>
<td>5-Fluorouracil</td>
<td>None</td>
<td>16</td>
<td>12.5</td>
<td>285</td>
<td>8.0</td>
<td>0.46</td>
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<td>7</td>
<td>02-06-12</td>
<td>51</td>
<td>F</td>
<td>24</td>
<td>22</td>
<td>None</td>
<td>None</td>
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<td>166</td>
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<td>9</td>
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<td>5</td>
<td>Chlorambucil</td>
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<td>43</td>
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<td>53</td>
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<td>Steroid x-ray</td>
<td>Septicemia,</td>
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<td></td>
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<td></td>
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<td>12</td>
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<td>26</td>
<td>13</td>
<td>HN₂ x-ray Chlorambucil</td>
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<td>7.8</td>
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<td>13</td>
<td>02-06-19</td>
<td>32</td>
<td>M</td>
<td>54</td>
<td>42</td>
<td>Cortisone</td>
<td>None</td>
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<td>Asthma</td>
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<td>57</td>
<td>M</td>
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<td>6</td>
<td>None</td>
<td>Bronchitis</td>
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<td>12.9</td>
<td>188</td>
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<td>17</td>
<td>01-93-67</td>
<td>60</td>
<td>M</td>
<td>84</td>
<td>36</td>
<td>Chlorambucil</td>
<td>Septicemia,</td>
<td>7.3</td>
<td>14.0</td>
<td>65</td>
<td>2.9</td>
<td>1.05</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Bronchitis.</td>
<td>7.3</td>
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<td>1.05</td>
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<td>M</td>
<td>84</td>
<td>84</td>
<td>Prednisone</td>
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<td>13.4</td>
<td>155</td>
<td>2.0</td>
<td>1.0</td>
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</table>
With the exception of one patient (psychotic depression), symptomatic improvement, in terms of an improved sense of well being and increased strength and appetite, was uniformly observed. Following cessation of prednisone symptomatic improvement persisted in 12 patients. This would seem to indicate that their symptomatic improvement was at least, in part, related to the antileukemic effect of prednisone.

The regressions in splenomegaly were often dramatic (fig. 1). Comparable regressions of lymphadenopathy and hepatomegaly occurred and, in the majority of the patients, it was no longer possible to palpate previously enlarged lymph nodes, liver, or spleen (table 4). However, the duration of this effect was brief in that 70 per cent of the patients had recrudescence of leukemic activity as evidenced by enlarging spleen and liver before the end of prednisone therapy or within four weeks of cessation of prednisone therapy.

In 16 of the 18 patients a rapid increase in the total white count occurred during prednisone administration (fig. 2). The white count elevations were

**Fig. 1.—Chronic lymphocytic leukemia: effect of prednisone on spleen size.**
often very striking and ranged up to a rise of 270,000 cells per mm$^3$ with a median maximum increase of 40,000 cells per mm$^3$. This increase in the white count was noted early, the maximum occurring at two weeks, and could be almost entirely accounted for by an increase in lymphocytes. Subsequently the white count gradually fell reaching pretreatment values at the end of prednisone therapy and two months later were significantly below pretreatment values. Thus the antileukemic effect was discordant in that infiltration
of the spleen, liver and lymph nodes decreased whereas leukemic "infiltration" of the blood increased. Moreover, these discordant effects tended to parallel each other in time in terms of maximal changes and in that the return of the white count to pretreatment levels was usually associated with recrudescence of organ infiltration. Only two of the 18 patients had a progressive fall in their white counts from the onset of therapy.

The changes in hemoglobin, reticulocytes, and platelets which occurred with prednisone are shown in figure 3. All but one patient had a progressive rise in hemoglobin concentration. Prompt cessation of hemolysis occurred in the one who had a symptomatic hemolytic anemia. Associated with the hemoglobin increases, a reticulocytosis was observed. The platelet count also tended to rise with prednisone. Two patients with platelet counts of 11,000 and 20,000 respectively had a gradual return of their platelet counts to normal. In contrast to the changes in organomegaly some of the above mentioned hematologic improvements persisted for more than eight weeks after cessation of prednisone therapy (fig. 3). Neutropenia was present in nine patients before treatment. On prednisone a rapid rise in the absolute neutrophil count was observed, often to above normal levels (fig. 4). By the end of the 12 week treatment program, only one patient remained neutropenic. However, by the 8th week after steroid therapy the median neutrophil count had returned to 3,000 cells per cu. mm.

In an attempt to elucidate better the rapidity of the effect of prednisone on the peripheral white count, four patients were given rapid intravenous infusions of 100 mg. of prednisolone hemisuccinate at the start of treatment. The white count was determined at 15 minute intervals for the first hour and at two hour intervals for the next 12 hours. No significant change in the total white count was observed during the first 60 minutes. Thus there is no evidence that the intravenous administration of prednisolone acutely elevates the white count.

Bone marrow aspirations were performed on six patients, five of whom had moderate peripheral hematologic improvement and marked regression of organ infiltration. In four of the six patients there was a definite increase in the myeloid and erythroid elements. It was difficult to quantitate the marrow leukemic infiltrate in these patients because of multifocal or patchy distribution. In every case, in spite of marked decrease in spleen and lymph node size, the mature lymphocyte remained the predominant cell in the marrow. In three patients, the extent of the leukemic infiltrate was considered unchanged, in

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Number with Finding at Onset of Prednisone Therapy</th>
<th>Prednisone Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete Regression</td>
<td>Partial Regression</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>16</td>
<td>9</td>
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<tr>
<td>Splenomegaly</td>
<td>12</td>
<td>6</td>
</tr>
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</table>
two there was a moderate decrease and, in one, there was an increase during prednisone therapy.

The changes in gamma globulin during prednisone therapy were striking in their variability (fig. 5). There was some tendency for normal or high values to fall and for low values to rise during the first four weeks of therapy and in addition there was a slight fall in the median values during the 12 weeks of therapy. Changes in the gamma globulin for individual patients could not be related to clinical or hematologic alterations.

The three patients who had previously received adrenal corticosteroids all had significant improvement with prednisone. After completion of the
PREDNISONE THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA

Fig. 4.—Chronic lymphocytic leukemia: effect of prednisone therapy on absolute neutrophil count.

Prednisone study, three additional patients were given repeat courses of prednisone. Antileukemic responses, similar in degree and duration to their previous effect, were again noted.

INFECTIONS

Thirteen infections occurred in 12 patients during the study (tables 3, 4). The frequency of infection was one in every 311 patient-days in the control
CHRONIC LYMPHOCYTIC LEUKEMIA:
EFFECT OF PREDNISONE ON GAMMA GLOBULIN

Fig. 5.—Chronic lymphocytic leukemia: effect of prednisone on gamma globulin.

phase and one in every 189 patient-days in the prednisone period. This difference in frequency is not significant ($P > 0.05$) by chi square test.

Infections were generally more severe and more difficult to control when the patients were receiving prednisone. The median duration of fever was 4.5 days in the prednisone period and only two days in the control period. The sites of infection and causative organisms for the prednisone and control periods (table 4) indicate a greater severity of infection in the patients receiving prednisone. Two fatal infections occurred. The first of these was an
 overhearing bacterial pneumonia in a 74 year old man. He had previously experienced bronchopneumonia during the control period which had promptly responded to antibiotics. The second patient died with miliary tuberculosis. A second instance of reactivation of tuberculosis occurred in a man who had old pulmonary calcifications and a positive tuberculin skin test. While receiving prednisone he developed an intermittent low grade fever and then insidiously, a hemorrhagic pleural effusion. Cultures of the sputum and pleural fluid were negative for the tubercle bacillus, but six weeks after fever began the diagnosis of tuberculosis was established by pleural biopsy. The patient
with herpes genitalis is of interest in that the skin lesions progressed while prednisone was continued for three weeks. Upon cessation of prednisone the lesions gradually healed.

Certain untoward effects presumably related to prednisone administration were noted. They did not differ qualitatively from the side effects occurring in the corticosteroid therapy of other disorders and consisted of anxiety, insomnia, leg cramps, gastrointestinal distress, congestive heart failure and one instance of psychosis. There was a total of 18 such episodes, the majority of which were mild and easily controlled by appropriate therapy. Complete subsidence of symptoms invariably occurred with cessation of prednisone administration. In only one instance (psychosis) was it necessary to discontinue drug therapy. None of four patients with "gastrointestinal distress" had radiologic evidence of duodenal ulceration. The patient who expired with pneumonia was found to have multiple bleeding duodenal ulcers which were not suspected clinically.

**Discussion**

The antileukemic effects achieved were comparable to those previously described. They often were quite striking clinically as well as dramatic for the patients who not infrequently requested repeat corticosteroid treatment in follow up visits. Not only were the improvements transient but also in no instance was the leukemic remission complete since bone marrow aspiration continued to show marked infiltration. Others have recorded an instance of reversion of marrow to normal with steroid therapy. However, as lymphocyte "invasion" of the marrow is usually patchy in chronic lymphocytic leukemia, it can be most difficult to quantitate.

The marked elevation of the absolute lymphocyte count despite regression, often complete, of organ infiltration has been previously observed and remains unexplained. In patients without hematologic disorders corticosteroid administration produces a lymphopenia as well as decrease in lymphatic tissue. In acute lymphatic leukemia marked reduction of circulating and tissue leukemic cells is the usual result of corticosteroid therapy. The increase in WBC and decrease in organ size were correlated in that the maximum changes and regression towards pretreatment values tended to be concurrent. However, the magnitude of the changes, that is, the correlation of change in organ size and change in the WBC was not good. Calculation based on leukocrits, estimated blood volume, and estimated volume of leukemic cells in the spleens suggested that the increase in white blood count could not account for the decrease in organ size. Thus, though lymphocyte redistribution undoubtedly occurs, it cannot account completely for the decrease in organ size. Thus, some degree of lympholysis must also occur.

The present study indicated strongly but not conclusively that the administration of prednisone to patients with chronic lymphocytic leukemia increases the frequency and severity of infections. It should be emphasized that the 18 patients in this study were ambulatory and not in the advanced stage of their disease. Presumably the prolonged administration of adrenal corticosteroids or their use in patients with more advanced disease would
result in an even greater number of severe infections. It is noteworthy that Yunis and Harrington recorded three infections in 11 patients with chronic lymphocytic leukemia treated with methylprednisolone and that one of these, a staphylococcal pneumonia, was fatal. In addition, Pearson et al. observed one case of fatal varicella in four patients treated with ACTH. Close observation of patients receiving prednisone and prompt treatment of their infections is imperative. Fever in the absence of infection is rare in patients with chronic lymphocytic leukemia. The reactivation of tuberculosis in two patients receiving prednisone would indicate that the use of antituberculous agents prophylactically ought to be considered, particularly in the presence of a positive tuberculin reaction or pulmonary lesions.

Hypogammaglobulinemia and decreased circulating antibody production occur frequently in patients with chronic lymphocytic leukemia and are largely responsible for the increased susceptibility to infection. Though, taken as a whole, the gamma globulin values fell during corticosteroid administration this change was slight and was, in view of the variability of gamma globulin levels within the individual patient, not significant.

X-irradiation and alkylating agents, particularly chlorambucil, remain the treatment of choice for chronic lymphocytic leukemia. Corticosteroids, because of the brief duration of the remission induced and the increased risk of infection, should be reserved for patients with complicating hemolytic anemia and/or thrombocytopenia, and for patients with refractory disease who have bone marrow failure.

SUMMARY

A study of prednisone therapy in 18 patients with chronic lymphocytic leukemia is reported.

1. Antileukemic effects consisting of subjective improvement, decrease in organ infiltration, improvement in hemoglobin and absolute neutrophil count occurred.

2. These effects were transient.

3. An increase, often marked, in the number of circulating lymphocytes occurred in 16 of the 18 patients.

4. The administration of prednisone was attended by an increase in the severity of infections. Some increase in the frequency of infections was also observed, but this was not statistically significant (p > 0.05).

It is concluded that corticosteroids should not be used electively in patients with chronic lymphocytic leukemia except in the presence of hemolytic anemia, significant thrombocytopenia or in the presence of advanced disease associated with bone marrow failure.

SUMMARIO IN INTERLINGUA

Es reportate un studio de therapia a prednisona in 18 patientes con chronic leucemia lymphocytic.

1. Esseva constatate effectos antileucemic que consisteva de melioration subjective, reduceite intensitate del infiltration de organos, melioration de hemoglobinina, e melioration del numeration absolute de neutrophilos.
2. Iste effectos esseva transitori.
3. Un augmento—frequentemente marcate—occurreva in 16 del 18 patientes in le numero del circulante lymphocytos.
4. Le administration de prednisona esseva accompaniate in un augmento del severitate de infectiones. Etiam un certe augmento del frequentia de infectiones esseva observate, sed isto non esseva statisticamente significative (p > 0.05).

Es concludite que corticosteroides non deberea esser usate electivemente in patientes con chronic leucemia lymphocytic, excepte in le presentia de anemia hemolytic, de grados significative de thrombocytopenia, o in le presentia de morbo avantiate in association con decompensation del medulla ossee.

REFERENCES
3. —, and —: Use of pituitary adrenocorticotropic hormone (ACTH) and cortisone in lymphomas and leukemias. J.A.M.A. 144:1349, 1950.
PREDNISONE THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA

Hospital 95:197, 1956.


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Regulated intravenous doses of quinidine produced thrombocytopenia without clinical sequelae. A method for estimating a safe test dose is described. The degree of thrombocytopenia was dependent upon the plasma concentrations of quinidine and antibody. By relating these data to concurrent in vitro tests, it was concluded that the amount of antibody which attaches to platelets when thrombocytopenia develops is too small to produce platelet agglutination or even complement fixation. Hence the minimal amount of antibody attached to the platelets probably increases their susceptibility to normal sequestration.

M. B. Z.
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