A Randomized Comparison of Two Doses of Human Lymphoblastoid Interferon-α in Hairy Cell Leukemia

By Richard V. Smalley, Susan A. Anderson, Richard L. Tuttle, Joseph Connors, Linda M. Thurmond, Andrew Huang, Karol Castle, Charles Magers, and John K. Whisnant for The Wellcome HCL Study Group

One hundred thirty-eight patients with hairy cell leukemia were randomized to receive either a dose of 2.0 megauinits (MU)/m² or a 10-fold lower dose of 0.2 MU/m² of a highly purified natural α-interferon, administered daily for 28 days followed by a three times a week schedule. Ninety-seven of these patients had previously undergone splenectomy, but otherwise none of the patients had received prior therapy for their leukemia. The two doses were comparable in their effect on improving the neutrophil and platelet count, whereas the higher dose had a greater beneficial effect on the hemoglobin level and a greater antileukemic effect on the marrow. Acute toxicity in the form of a flu-like syndrome, neurologic side effects, neutropenia, and the need for platelet transfusions was observed less frequently in the low-dose group, as was the chronic fatigue syndrome. No neutralizing antibody activity was seen in the sera from 81 patients examined. Because of its beneficial effect on the neutrophil and platelet count and a lower degree of toxicity (ie, a superior therapeutic/toxicity ratio), the low dose is recommended as initial therapy in patients with hairy cell leukemia. This therapy may be followed by dose escalation once clinical improvement is observed.

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PATIENTS AND METHODS

In this multi-institutional study, patients with active HCL were randomized centrally by telephone between a dose of either 2.0 megauinits (MU)/m², herein referred to as the standard dose, or 0.2 MU/m², herein referred to as the low dose (1 MU = 10⁶ IU). After dose assignment, patients received IFN-α-N1 daily subcutaneously (SC) for 28 days, followed by a three times a week (tiw) schedule until maximal clinical response. After 6 and 12 months of treatment, patients were evaluated for therapeutic efficacy. After 6 months of treatment, those patients who had not achieved a partial response (PR) were to undergo dose escalation in three steps over a 6-week period. Patients receiving the low dose were to escalate to a dose of 2.0 MU/m², while those receiving 2.0 MU/m² as a starting dose were to escalate to a dose of 10 MU/m².

Eligibility criteria included morphologic confirmation of HCL, prior splenectomy (or medical contraindication or patient refusal), and measurable disease as manifested by peripheral cytopenia, infiltration of BM, circulating hairy cells, measurable lymphadenopathy, or organomegaly. Ineligibility criteria included an active...
infectious process; pregnancy; significant cardiovascular disease
defined as New York Heart Association functional class III or IV;
other pulmonary, gastrointestinal, or renal conditions that might
imply the tolerance to the acute pyrexial reaction associated with
IFN administration; a known sensitivity to neomycin or polymyxin
B; severe malnutrition, severe nausea, or frequent vomiting;
chronic drug or alcohol addiction; or a history of a second
malignancy, excluding basal cell carcinoma or carcinoma in situ of
the uterine cervix. In practice, all of these ineligibility criteria,
except pregnancy, were considered relative contraindications and
were balanced, in the judgment of the investigators, by the
chronic drug or alcohol addiction; or a history of a second
malignancy, excluding basal cell carcinoma or carcinoma in situ of
the uterine cervix. In practice, all of these ineligibility criteria,
except pregnancy, were considered relative contraindications and
were balanced, in the judgment of the investigators, by the
potential benefit from treatment. As discussed below, 18 patients
with infection, cardiac disease, or cirrhosis were entered despite
these contraindications.

After giving informed consent, patients were centrally randomly
assigned by telephone to receive either 2.0 MU/m², or the low
dose, 0.2 MU/m², using a permuted block with 10 patients per
block. This randomization procedure allowed for an equal number
of patients to be randomized to each treatment after every 10
entries. The blocks were designed and the sequences assigned by
Clinical Statistics of Burroughs Wellcome Co. Separate sequences
were used for the United States and the Canadian entries.

During treatment, patients periodically underwent hematologic,
clinical, and chemical evaluations. Data collection forms (DCFs)
were reviewed centrally and major contributing institutions were
site visited and audited for data accuracy. Data were entered into
the VAX computer system of the University of Wisconsin Biostatis-
tics Center (UWBC) and were analyzed using a SAS program by
the UWBC. Response criteria included a complete response (CR)
defined by a normal peripheral blood (PB) count, including a
hemoglobin (Hb) greater than or equal to 12 g/dL, a neutrophil
count greater than or equal to 1,500/mm³, and a platelet count
greater than or equal to 100,000/mm³; a normal BM (defined as a
marrow without leukemic infiltration on microscopic review of the
biopsy and with demonstrable hematopoiesis); and a normal
physical and radiologic examination. A PR was defined by a BM
with a 50% decrease in the hairy cell index (HCI) and demonstra-
table hematopoiesis plus hematologic and physical examination
criteria as above. A PR hematologic (PRH) was defined as
normalization of PB as defined above but less than a 50% decrease
in the HCI. Patients in whom all three PB elements did not
improve to normal were categorized as either stable (completing 12
months of treatment) or treatment failure (off study before
response was also performed centrally based

RESULTS
One hundred thirty-eight patients were entered on study between January 1, 1985 and October 24, 1986 by 30
different investigators from 27 institutions. Demographic data are summarized in Table 1.

Sixty-nine patients were randomized to each of the two
doses. Five of the 138 patients were considered ineligible
for antitumor efficacy. Three patients received no treat-
ment (one randomized to the low dose and two randomized
to the standard dose); one patient randomized to the
standard dose was subsequently determined to have non-
Hodgkin's lymphoma and adequate data were unavailable
for one patient randomized to the standard dose. There-
fore, 65 of the 69 patients randomized to the standard
dose and 68 of the 69 patients randomized to the low dose were
considered evaluable for antitumor efficacy. Data from
these same 133 patients were used in the toxicity analysis.

Eighteen patients were entered on study despite failure
to meet the eligibility criteria. Eleven patients had active,
chronic severe infections, two had cirrhosis with substantial
complications, and five had active coronary artery disease
(angina). Twelve of these patients were randomized to the standard dose and six to the low dose. Using intent to treat as a basis for analysis, these ineligible patients were considered evaluable and included in the final analyses. Six of these patients (all randomized to the standard dose) obtained an objective response, two received 12 months of treatment (one on each arm) without obtaining a response, and 10 failed treatment or were removed from study early because of toxicity. The likelihood of a response in these patients was less than in the remainder of the patient population, regardless of dose.

Eight of the entries on the standard dose and five on the low dose died within the first 12 months of study. Nine of these 13 patients (five on the standard and four on the low dose) were among those entered despite contraindications. An additional eight patients died during the period of time beyond the initial 12 months of treatment, three on the standard-dose and five on the low-dose arm. All other patients remain alive as of last follow-up. Several patients on both arms received intermittent or continuous α-IFN therapy beyond the initial 12-month period of protocol treatment. None have received other treatment (including deoxycoformycin or 2-chlorodeoxyadenosine) during the period of observation.

Survival curves for each of the arms, including all 133 evaluable patients, are presented in Fig 1. There are no differences noted. Considering only those patients who were eligible and evaluable, there have been six deaths in the 53 eligible and evaluable patients randomized to the standard arm and six deaths in the 62 eligible and evaluable patients randomized to the low-dose arm. These differences are not statistically significant. Randomization to low-dose IFN did not compromise survival.

Therapeutic effect on PB elements. Tables 2 through 4 present by treatment group data indicating improvement in Hb level, neutrophil count, and platelet count during the first year of treatment. The tables provide by month on treatment the mean and standard deviation for all patients for whom data were available at each time point. In addition, the tables also provide the mean percent change from baseline obtained by paired comparison for each time point. The percent change for each patient at each time point compared with baseline was obtained and the mean overall percent change was then obtained for each time point and is provided as mean percent change in the tables. Data are included by month for all patients on whom a blood count was performed at least once between days 20 and 40, 50 and 70, and 80 and 100 for months 1, 2, and 3, respectively, and for similar time periods for months 6, 9, and 12. Kaplan-Meier plots display the time to improvement in Hb, neutrophil, and platelet counts (Figs 2 through 4). The difference in the effect of the two doses on the time for the Hb level to return to normal was statistically significant (P < .05) in favor of the standard dose but the difference in the effect on both neutrophil and platelet return was not. The curves for the return of the platelet count were superimposable, while the curves for the return of the neutrophil count were slightly but neither statistically nor clinically significantly different.

With the exception of a larger requirement for RBC transfusions in the low-dose group during months 4 to 6 and a twofold greater need for platelet transfusions during the first 3 months by the standard-dose group, there was no difference in transfusion requirements during the period of study (12 months) between the two groups. More infections occurred in more patients receiving the standard dose during the first 3 months, while the opposite trend occurred during months 4 through 9. Table 5 provides a summary of these data.

Evaluation of antitumor effect. Slides from BM core biopsies were available for review from most patients who were entered on treatment. After 12 months of treatment, 44 of 65 evaluable patients (68%) receiving the standard dose achieved a 50% or greater decrease in marrow infiltration, including 21 who had complete clearance. In contrast, 34 of 68 (50%) evaluable patients receiving the low dose obtained a 50% or greater decrease, including 12 who had complete clearance. This difference is statistically significant (P = .05, two-tailed Fisher's exact test). Forty of 53 eligible and evaluable patients receiving the standard dose
obtained a response rate after therapy without benefit of dose escalation. Forty-six patients, or 48% of the evaluable patients receiving the standard dose, had detectable binding antibody at initiation of IFN treatment. Seven of these patients developed detectable neutralizing antibodies. Five patients of the seven obtained a marrow response. Only one of these patients remained on treatment beyond 6 months of therapy; 19 improved their quality of response after escalation. Sixteen patients randomized to the low dose who were eligible for dose escalation did not undergo dose escalation. Seven of these patients achieved a major response between 6 and 12 months of therapy without benefit of dose escalation.

Antibodies to IFN. The sera from 61 patients were evaluated for antibody formation to α-IFN, 43 receiving the standard-dose regimen and 18 receiving the low-dose regimen. Serum specimens were screened for binding antibody and assayed for neutralizing activity. Patient serum was evaluated for antibody in specimens obtained at a median of 472 days (standard dose) or 406 days (low dose) after initiation of IFN α-N1 therapy.

None of the 61 evaluable patients treated with IFN α-N1 developed detectable neutralizing antibodies. Five patients on the standard dose had detectable binding antibody at 79 months of treatment. The difference in response rate after 12 months of therapy was not statistically significant. Forty of 53 (75%) evaluable patients receiving the standard dose and 39 of 62 (63%) of evaluable patients receiving the low dose obtained an objective major response.

Splenectomized versus nonsplenectomized patients. Twenty-two patients receiving the standard dose had not undergone splenectomy before entering this trial. Four obtained a CR, four a PR, and three a PRH. Nineteen patients randomized to the low dose had not previously undergone splenectomy. Three achieved a CR, five a PR, and one a PRH. The combined response for patients treated on study who had not previously undergone splenectomy was seven CRs, nine PRs, and four PRHs for an overall response rate of 20 of 41 (49%). This response rate is less than the rate of 65 in 92 (71%) patients who had been previously splenectomized (P = .02, two-tailed Fisher's exact test).

Dose escalation. Seven patients randomized to the standard dose underwent full dose escalation, two during the first 6 months of treatment. Four of the seven patients benefited with an improvement in their PB count to normal and three of the seven obtained a marrow response.

Four patients randomized to the low dose underwent dose escalation with therapeutic intent during the first 6 months of treatment but none obtained clinical benefit. Only one of these patients remained on treatment beyond 6 months. Thirty-one patients underwent dose escalation during the second 6 months of study; 19 improved their quality of response after escalation. Sixteen patients randomized to the low dose who were eligible for dose escalation did not undergo dose escalation. Seven of these patients achieved a major response between 6 and 12 months of therapy without benefit of dose escalation.

Overall response. Forty-eight percent of the evaluable patients on the standard dose (95% confidence interval [CI], 35% to 60%) and 25% of the evaluable patients on the low dose (95% CI, 15% to 37%) achieved an objective major (CR, PR, PRH) response after 6 months of therapy (P = .01, two-tailed Fisher's exact test). Forty-six patients, or 71% (95% CI, 58% to 81%), receiving the standard dose and 39 patients, or 57% (95% CI, 45% to 69%), receiving the low dose achieved an objective major (CR, PR, PRH) response after 12 months of treatment. The difference in response rate after 12 months of therapy was not statistically significant. Forty of 53 (75%) evaluable patients receiving the standard dose and 39 of 62 (63%) of evaluable patients receiving the low dose achieved a 50% or greater decrease in marrow infiltration.

Table 2. Mean Hb Values (g/dL) by Month

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*By paired comparison.

Table 3. Absolute Neutrophil Values by Month

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<td>51</td>
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<td>37</td>
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*By paired comparison.

†Paired comparison on 58 patients shows a 16% increase, although the mean of month 1 is decreased from the mean of month 0.
DOSE EFFECT OF α-IFN IN HCL

Table 4. Platelet Values by Month

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<td>53</td>
<td>55</td>
<td>46</td>
<td>41</td>
<td>35</td>
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<tr>
<td>Mean (K/mm³)</td>
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<td>231</td>
<td>235</td>
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<td>137</td>
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<td>233</td>
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<td>60</td>
<td>51</td>
<td>46</td>
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<tr>
<td>Mean (K/mm³)</td>
<td>112</td>
<td>131</td>
<td>169</td>
<td>174</td>
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<td>223</td>
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<td>SD (K/mm³)</td>
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<td>97</td>
<td>101</td>
<td>96</td>
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Values are in thousands per cubic millimeter.
*By paired comparison.

To 578 days after beginning therapy. One patient on the low dose developed binding antibody that was detected on day 253. None of these binding antibodies neutralized IFN. Three of the six patients converted to negative for binding antibody in subsequent specimens.

Toxicity. IFN α-N1 was well accepted and reasonably well tolerated by patients at either dose level, although the incidence of side effects was greater in those receiving the standard dose. Table 6 presents the number of patients developing a grade 3 level of toxicity using the National Cancer Institute (NCI) Common Toxicity Criteria. The following definitions of grade 3 toxicity were used: chills, presence of rigors; fatigue, less than 50% Karnofsky performance status; malaise, greater than 24 hours’ duration; nausea and vomiting, emesis despite antiemetics; headache, lasting greater than 24 hours; fever, greater than 39.7°C. Flu-like symptoms were greater, both quantitatively and qualitatively, among those receiving the standard dose. These symptoms invariably occurred during the first 4 to 8 weeks of treatment and then gradually abated as the patient developed tolerance.

Neurologic toxicity also occurred to a greater degree and with greater frequency in patients receiving the standard dose. These side effects were grouped roughly into three categories: mental depression, dizziness, and peripheral neuropathy. There were four episodes of grade 3 cardiac toxicity in patients who received the standard dose, three in patients who were ineligible because of preexisting cardiac disease. One patient with preexisting coronary artery disease developed congestive heart failure after the first dose of treatment and was removed from study. Two other patients died suddenly after 1 and 9 months of treatment, both presumably cardiac deaths. The patient who died after 1 month of treatment had preexisting coronary artery disease. The fourth episode of grade 3 cardiotoxicity, also in a patient with preexisting cardiac disease, was a myocardial infarction that occurred on day 38 of treatment. The patient recovered and continued IFN therapy without further problems. One patient who received the low dose was listed as having cardiac toxicity. He was in extremis when he began treatment and died within 3 weeks of initiating treatment. The cardiac disorder in this patient was thought to be disease-related rather than treatment-related.

One patient receiving the standard dose developed pneumonia associated with neutropenia induced by IFN α-N1 during the first 2 weeks of therapy and died. His neutrophil count had been normal before treatment. There was a higher incidence of neutropenia (<500/mm³) and infection during the first month of treatment in the standard-dose group. Forty-one of the 65 evaluable patients had

Fig 2. A Kaplan-Meier plot of the time to first reach a normal (12 g/dL or greater) Hb. (-----) Standard dose, 2.0 MU/m²; (——) low dose, 0.2 MU/m².
neutropenia during the first month of therapy, an incidence of 63%, while 20 of the 65 evaluable patients developed a bacterial infection in the first or second month of treatment, an incidence of 31%. Nearly all of the patients developing an infection did so with a neutrophil count less than 500/mm$^3$. Thirty-one of 68 evaluable patients on the low dose had neutropenia during the first month of therapy, an incidence of 46%, while 12 of the 68 developed a bacterial infection during the first 2 months, an incidence of 18%. The incidence of neutropenia ($<500$/mm$^3$) was significantly greater in the standard-dose arm ($P = .055$).

Anorexia, malaise, elevated SGOT, and thrombocytopenia, in addition to neutropenia, were all more frequent in patients receiving the standard dose.

Seven patients who received the standard dose underwent dose reduction: three because of worsening thrombocytopenia, two because of fever and infection, and one each for increasing SGOT and gastrointestinal (GI) complaints. Two patients receiving the low dose underwent dose reduction: one because of an increase in SGOT and one because of persistent thrombocytopenia. These problems occurred early in the course of treatment. All other patients tolerated the 12 months of treatment without difficulty. There were six reported instances of long-term chronic fatigue syndrome in patients receiving the standard dose; none were reported in patients receiving the low dose.

**DISCUSSION**

Quesada et al determined early in their studies that a dose of 12 MU/m$^2$ of recombinant α-IFN was not tolerable in patients with HCL. Subsequently, they showed that a dose of 2.0 MU/m$^2$ was both well tolerated and effective and this dose, administered tiw, has become the standard dose. The present study shows that a highly purified natural α-IFN at a dose of 2.0 MU/m$^2$ administered daily for 28 days is well tolerated in most patients with HCL, but suggests that this dose might be dangerously myelosuppressive in some, neurotoxic in others, and cardiotoxic in patients with previously existing coronary artery disease.
lower dose of 0.2 MU/m², also administered daily for 28 days, was better tolerated, induced improvement in the peripheral neutrophil and platelet counts of patients as rapidly as did the standard dose, and warrants consideration as the initial therapeutic dose for this product in all patients.

Patients with HCL frequently present in a compromised condition. Many are neutropenic and susceptible to serious infection. α-IFN is a myelosuppressive agent and in this study at a daily dose of 2.0 MU/m² induced neutropenia (<500/mm³) frequently associated with bacterial infection in a greater number of patients during the first 4 to 8 weeks of treatment than did the lower dose. Likewise, during this period, twice as many patients receiving the standard dose required platelet transfusions. Glaspy et al have shown in a small pilot trial involving four patients that granulocyte colony-stimulating factor administered in conjunction with primary treatment might rapidly increase the absolute neutrophil count in patients with HCL. Such an approach would counterbalance the significantly greater degree of neutropenia, but not thrombocytopenia, induced by a dose of 2.0 MU/m².

α-IFN may also induce fever and chills during the early weeks of administration and at a dose of 2.0 MU/m² did so more frequently than did the lower dose in this study. It is also known to induce cardiac side effects, especially in patients with preexisting cardiac disease and did so at a dose of 2.0 MU/m² in this study. It must be realized that this study was performed during the early days of the use of α-IFN as treatment for HCL. There were many patients in whom the disease had been progressing in severity and who were in serious condition with their leukemia. These patients, because there was no other treatment option at the time, were entered on this study despite relative contraindications because it was felt that the prognosis of their leukemia was bleak.

This study has shown that both the neutrophil count and the platelet count respond rapidly to either the standard- or the low-dose regimen. Substantial clinical improvement, primarily in terms of increased platelet and neutrophil counts, was observed within the first 4 to 8 weeks of treatment in patients receiving the low dose. This gain was obtained at a lower price in terms of cardiac and neurologic toxicity, flu-like syndrome, myelosuppression, the need for platelet transfusion, and incidence of bacterial infections. Once such improvement has been obtained and patients have developed tolerance to the acute toxicity associated with α-IFN, the dose may then be increased to obtain the significantly greater antileukemic effect of the higher dose. In this study, the dose was escalated after 6 months of treatment. This escalation could be performed earlier, perhaps after 3 months of induction therapy, without difficulty. Tolerance to the side effects associated with IFN has been well documented previously.

The experience in this study with the low dose confirms the early nonrandomized experience of Gastl et al regarding its effect on platelet and neutrophil counts. Using a recombinant molecule administered daily for 3 months, they showed a rapid resolution of thrombocytopenia in 20 of 21 patients and of neutropenia in nearly all patients. After 4 weeks of treatment, the median neutrophil count was approximately twice that of a group of patients treated with the standard dose (historic control). They reported minimal toxicity with the low dose. Moormeier et al and Thompson et al reported on their single institutional experience while Golomb et al have recently summarized the multi-institutional experience (including the two single institutions) with a low dose of IFN α-2B. The multi-institutional results indicate a major response (CR, PR, PRH) in 11 of 49 patients. This rate of 22% is similar to our response rate of 25% with the low dose regimen observed after 6 months of treatment. They, likewise, report minimal toxicity. It seems clear from our experience, plus that of Gastl et al, that a low dose of α-IFN will improve the platelet and neutrophil counts in a majority of patients in a short (6 to 12 weeks) period of time with significantly less toxicity. It is also clear that there is a dose-response effect and a higher dose of α-IFN will induce a qualitatively greater response that, presumably, might last longer. Thus, even though the overall response rate is low in patients continued on low-dose therapy, a low dose should be considered as initial therapy followed by an increase in dose over time.

No patients in this study produced detectable neutralizing antibodies to IFN. Previous studies in Europe with IFN α-N1 showed a lack of neutralizing antibody formation in 75 patients with HCL. However, the clinical significance of neutralizing antibodies, especially in patients with HCL, is not clear. Earlier reports suggested an association between the development of neutralizing antibodies and relapse, but

<table>
<thead>
<tr>
<th>Table 5. Number of Transfusions and Infections During Treatment by Evaluable Patients</th>
<th>Months</th>
<th>0-3</th>
<th>4-6</th>
<th>7-9</th>
<th>10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC transfusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard dose</td>
<td></td>
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<td></td>
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</table>

<table>
<thead>
<tr>
<th>Table 6. Incidence of Observed Severe Side Effects in Eligible and Evaluable Patients</th>
<th>Standard Dose (N = 53)</th>
<th>Low Dose (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Chills</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Malaise</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>N/V</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Neurologic</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Patients with grade 3-4 side effects</td>
<td>27</td>
<td>51</td>
</tr>
</tbody>
</table>
recent experience suggests that neutralizing antibodies may be short-lived and of no clinical significance.3,44

Patients with preexisting conditions that are relative contraindications to the use of α-IFN, such as central nervous system disease, active coronary artery disease, a history of cardiac arrhythmias, and active infection, but in whom therapy is needed despite this increased risk, would be expected to tolerate the lower dose with significantly less difficulty. However, in this study, none of the six patients with preexisting medical illnesses responded to the low dose.

It has been shown by this study that the dose of 0.2 MU/m² is better tolerated than is the dose of 2.0 MU/m². There were fewer episodes of the flu-like syndrome, fewer adverse drug effects, a lower incidence of myelosuppression, bacterial infections, and need for platelet transfusions, and no cardiac or neurologic toxicity with the lower dose. For these reasons, it seems reasonable to initiate treatment in patients with HCL with a dose of 0.2 MU/m² of α-IFN on a daily basis, decreasing this to three times a week after 1 month of treatment and then giving consideration to a dose escalation (to achieve a greater antileukemic effect) once improvement in the PB count has begun and tolerance to α-IFN has developed. Two other aspects of therapy for HCL to be considered include recommendations for splenectomy and appropriate combination drug therapy. Some nonsplenectomized patients in our study responded less than optimally to α-IFN and continued to show some degree of hypersplenism. Splenectomy, after months of IFN therapy, may improve the quality of response initiated by IFN in such patients. Secondly, deoxycoformycin has been shown to be a very effective but also a moderately toxic agent.27 As with α-IFN, a lower dose regimen of deoxycoformycin has also been shown to be effective and less toxic.24 The use of a low to moderate dose of α-IFN in patients, followed by deoxycoformycin once the PB count has improved, might be an appropriate way to combine these two effective agents. For a disease that was untreatable and incurable 5 years ago, there are now several approaches available and the challenge is how to best use them.

ACKNOWLEDGMENT

The following investigators contributed patients to this study: Dr A. Huang, Duke University; Dr J. Connors, Cancer Control Agency of British Columbia; Drs R. Weiner and W. Noyes, University of Florida; Drs W. Robinson and P. Bunn, University of Colorado; Dr K. Foon, University of Michigan; Dr P. Cassileth, University of Pennsylvania; Dr S. Horning, Stanford University; Dr A. Denes, Washington University; Dr M. Oken, University of Minnesota; Dr J. Goldsmith, University of Nebraska; Dr M. Flaum, Ochsner Clinic; Dr E. Nateson, University of Texas; Dr A. LoBuglio, University of Alabama in Birmingham; Dr C. Vogel, University of Miami; Dr O. Martello, University of Cincinnati; Dr L. Elias, University of New Mexico; Dr I. Walker, Hamilton (Ontario) Cancer Center; Drs R. Mansour and I. Troxell, Ft Gordon, GA; Dr W.R. Vogler, Emory University; Dr R. Krigel, Fox Chase Cancer Center; Dr P. Burns, University of Iowa; Dr J. Rinehart, Ohio State University; Dr L. Einhorn, University of Indiana; Dr C. Karanes, Wayne State University; Dr W. Friedenberg, Marshfield Clinic; Dr J. Bennett, Rochester Cancer Center; and Dr R. Stein, University of Tennessee. In addition, the efforts of a great many other people went into this study. The authors thank the many data managers, nurses, and investigators who participated in this study. In addition, we thank Judith Schiesel of Synertron, Inc, for her supervision of data management and Randi Sigal of Synertron, Inc, for typing and organizing this manuscript.

REFERENCES


33. Smalley RV, Tuttle RL, Wissman JK, Anderson SA, Huang AT, Robinson WA: Effectiveness of Wellferon at a dose of 0.2 MU/m² in the treatment of hairy cell leukemia. Blood 68:233a, 1986 (abstr, suppl 1)


A randomized comparison of two doses of human lymphoblastoid interferon- alpha in hairy cell leukemia. Wellcome HCL Study Group

RV Smalley, SA Anderson, RL Tuttle, J Connors, LM Thurmond, A Huang, K Castle, C Magers and JK Whisnant