Incidence of Response and Long-Term Follow-Up in Patients With Hairy Cell Leukemia Treated With Recombinant Interferon Alfa-2a

By Ellin Berman, Gienn Heller, Sanford Kempin, Timothy Gee, Ly-Le Tran, and Bayard Clarkson

Thirty-five evaluable patients with hairy cell leukemia (HCL) were treated with recombinant interferon alfa-2a (rIFN-α2a), given at a dose of 3 x 10^6 units (U) intramuscularly (IM) daily for 6 months followed by 3 x 10^6 UIM three times a week for an additional 18 months in a single institution study. All treatment was stopped after 24 months. Sixty-nine percent of patients achieved a partial response, 11% a minor response, and 3% (one patient) had stable disease. Six patients (17%) did not respond to therapy (range 9 to 32 months). Eleven patients had progression of their disease at a median of 10 months follow-up at a median of 20 months postcompletion of treatment variables measured after 2 years of treatment suggested that a low platelet count was associated with a high rate of disease progression. These findings are compared with other published trials using rIFN-α2b, a similar but not identical rIFN preparation. We conclude that while rIFN-α2a has a high overall response incidence, the rate of disease progression after therapy is discontinued approaches 50%, and that a subset of patients can be identified who are at high risk for recurrence after completing 2 years of treatment.

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From the Leukemia/Lymphoma Service, Department of Medicine, and the Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, Cornell University Medical Center, New York, NY; and the Department of Clinical Research and Development, Hoffmann-LaRoche Inc, Nutley, NJ.

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Address reprint requests to Ellin Berman, MD, Leukemia/Lymphoma Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

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progression of disease. Progression of disease was defined as a decrease in hemoglobin to less than 10 g/dL without clinical signs of bleeding, an increase in the WBC count to greater than 10,000 cells/μL or a decrease to less than 3,000 cells/μL, a decrease in the absolute neutrophil count to less than 1,500 cells/μL in three consecutive counts, or a decrease in platelets to less than 100,000 cells/μL.

Among the patients who completed 2 years of therapy, time to disease progression was defined as the interval from completion of therapy to any one of the abnormal hematologic parameters listed above. Patients who progressed with disease or died from complications of the disease while on therapy were considered primary failures.

Statistical analysis. Two statistical questions were asked in this study. First, were any pretreatment patient characteristics associated with a high probability of achieving maximum response, which in this trial was a PR? Second, were any posttreatment variables associated with a high rate of relapse after completion of the 2-year treatment program?

A univariate analysis of pretreatment WBC, hemoglobin, platelet count, percent bone marrow hairy cells, history of prior splenectomy, and history of prior drug treatment was performed using the score test statistic based upon the logistic regression model. Any variable that demonstrated a $P$ value $<.20$ based on the score test statistic was subsequently analyzed in a multivariate analysis using the logistic regression model. All variables that added information to the model at the .05 level of significance as measured by the maximum likelihood ratio test were included in the final model.

Because the time to relapse or death (disease free survival) in our data was compatible with the proportional hazards assumption between groups, the log rank test statistic was used. The following variables were analyzed: history of prior splenectomy or prior drug treatment, posttreatment WBC, hemoglobin, and platelet count, and residual bone marrow hairy cells measured at the end of 2 years of therapy. Any variable that demonstrated a $P$ value $.20$ based on the log rank test statistic was subsequently analyzed using a Cox proportional hazards regression analysis. All variables that added information at the .05 significance level were included.

Response duration and survival were calculated using the Kaplan-Meier method.

RESULTS

Clinical response. Between July, 1984 and July, 1986, 38 patients were entered on this study. Thirty-five patients are evaluable for response. Two patients who had lymphoid infiltrates in the bone marrow did not have HCL on retrospective review and an additional patient was lost to follow-up after 10 weeks of treatment.

Table 1 lists the pretreatment characteristics of the 35 evaluable patients. The majority of patients, 25 of 35 (71%), had either undergone a prior splenectomy or had received previous chemotherapy before trial entry. Ten patients (29%) had never received treatment for their disease. All patients were considered eligible for treatment because of significant mono- or pancytopenia as described above.

No patient achieved a pathologically documented CR. Twenty-four patients (69%) achieved a PR within a median of 148 days (range, 63 to 554). Four patients achieved an MR, and one patient had stable disease for 2 years. A total of 29 patients (83%) of the 35 evaluable patients therefore demonstrated some response to treatment.

Response according to prior treatment modality is outlined in Table 2. Approximately equal proportions of patients achieved a PR, regardless of whether they had undergone prior splenectomy, drug therapy, both, or neither.

Two patients died within 1 month of beginning treatment from complications arising from thrombocytopenia (central nervous system bleed) or neutropenia (overwhelming infection). Four patients did not manifest any significant response to rIFN-a2a and had progression of disease at 3.5, 5, 11.5, and 12 months, respectively, from start of treatment. Two of the patients who achieved a response (PR at 6 months and MR at 11 months) later developed progressive disease at 12 months and 23 months, respectively, despite continuation of therapy as per study design.

No specific clinical characteristics of these eight patients who failed while on treatment are apparent. Seven of these patients were males with a median age of 41 years (range, 33 to 64). Most were newly diagnosed and had presented for treatment within a relatively short time of diagnosis (median 8.5 months, range 1 to 30), and four patients had undergone prior splenectomy. As described in greater detail below, three of the four primary nonresponders (excluding the two patients who died early in their treatment course) developed detectable levels of neutralizing antibodies to rIFN-a2a while on treatment.

Toxicity. The majority of patients (75%) complained of fever, chills, myalgias, and malaise that responded to Tylenol and resolved spontaneously within 4 to 6 weeks. Only one patient was taken off rIFN-a2a because of presumed drug
A total of 12 patients, all of whom achieved a PR, have completed 2 years of treatment with rIFN-α2a and have maintained their initial response. The median time to PR in this group was 156 days (range, 71 to 282). No patient in this group developed neutralizing antibodies to rIFN-α2a.

The median duration of response for the entire group of 23 patients who completed 2 years of treatment is 25 months and is shown in Fig 1.

Survival. Overall survival for all 35 patients is shown in Fig 2 and demonstrates an 86% survival rate. Two patients died within 2 weeks of starting therapy from disease-related complications, one patient who was a primary nonresponder to rIFN-α2a at 12 months died from an infection after treatment with 2'-deoxycoformycin, and one patient died of infection during a reinduction attempt at time of relapse, which was 5 months from completion of the study (month 29). An additional patient died of a second malignancy 8 months after stopping rIFN-α2a (month 32).

Antibody response. Thirty-two of the 35 evaluable patients had at least two samples analyzed for the presence of neutralizing antibodies to rIFN-α2a. A total of six patients developed positive titers, three of whom were primary nonresponders. As outlined in Table 3, the antibody titers varied greatly among the six positive patients. Additionally, titers varied within the same patient when values were measured serially. For example, patient 2 had a drop in titer followed by a rise while on a three times per week injection schedule. Patient 3 had a rise in titer off all therapy; of interest is that his titer while on a daily injection schedule. Patient 5 had a positive titer that subsequently became negative as did Patient 6, who had a low initial titer. The median time from start of therapy to antibody formation was 7.5 months, range 6 to 16.

Analysis of prognostic variables. The score test suggested that initial WBC and prior splenectomy were prognostic factors for achieving a PR (Table 4). However, since both

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**Table 2. Response According to Prior Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Pts</th>
<th>PR</th>
<th>MR</th>
<th>S</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior splenectomy</td>
<td>22</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No prior splenectomy</td>
<td>13</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Prior drug</td>
<td>16</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No prior drug</td>
<td>19</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Prior splenectomy and prior drug</td>
<td>13</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Prior splenectomy and no prior drug</td>
<td>9</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No prior splenectomy and prior drug</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No prior splenectomy and no prior drug</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: Pts, patients; F, failure.

*See text for response criteria.
variables had a $P > .05$, neither was considered an important prognostic variable for achieving PR.

The log rank test was used to determine whether any prognostic factor, when analyzed individually, had an effect on remission duration. Five factors—history of prior drug therapy, WBC count, hemoglobin, platelets, and percent of residual hairy cells in a bone marrow sample performed after 2 years of therapy—met the cut off criteria ($P < .20$) based on the log rank test statistic (Table 4). However, further analysis suggested that one patient with an extremely high percent of residual marrow hairy cells had an overly influential effect on the log rank statistic relative to the other values ($n = 22$). Upon removal of this one value, percent residual marrow hairy cells no longer met the cutoff criteria. In this instance, the use of case deletion provided a more accurate interpretation of the bulk of our observation.

Cox's proportional hazards model was used to analyze the remaining four factors. This multivariate analysis separated platelet count from pretreatment drug therapy, white blood cell count, and hemoglobin, as the latter variables did not add further information to the model. Figure 3 predicts the disease free survival for a given posttreatment platelet count as derived from the Cox proportional hazards model. The curve begins to plateau at 25 months, which is the time of latest relapse, and predicts that patients with posttreatment platelet counts of less than 160,000 cells/$\mu L$ after 2 years of therapy will relapse within the following year.

In summary, no pretreatment factor(s) could be associated with the probability of achieving a PR. A low platelet count

### Table 4. Summary of Statistical Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ Value for Probability of Achieving PR*</th>
<th>$P$ Value for Rate of Disease Progression†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of prior splenectomy</td>
<td>0.169</td>
<td>0.372</td>
</tr>
<tr>
<td>Hx of prior drug treatment</td>
<td>0.667</td>
<td>0.123</td>
</tr>
<tr>
<td>WBC count</td>
<td>0.102</td>
<td>0.003</td>
</tr>
<tr>
<td>Hemoglobin count</td>
<td>0.367</td>
<td>0.085</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.462</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Bone marrow hairy cells</td>
<td>0.740</td>
<td>0.435</td>
</tr>
</tbody>
</table>

Abbreviation: Hx, history.

*Tests done on pretreatment values.
†Tests done on values measured after 2 years of therapy with rIFN-$\alpha2a$.

### Table 3. Characteristics of Patients Who Developed Positive Antibody Titers

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (yrs)/Sex</th>
<th>Prior Treatment</th>
<th>Time on rIFN-$\alpha2a$</th>
<th>Maximum Response</th>
<th>First + Follow-up Antibody Titer</th>
<th>Time to Disease Progression</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42/M</td>
<td>1983, splenectomy 12/84–11/85 (11.5 mos)</td>
<td>NR 9/85; 1:200 (9 mos)*</td>
<td>ND</td>
<td>Died from sepsis after DCF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>49/M</td>
<td>None</td>
<td>10/86–9/86 (11.5 mos)</td>
<td>NR 4/86; 1:25,600 (6 mos) 6/86; 1:2400 9/86; 1:25,600</td>
<td>—</td>
<td>CR on DCF</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>37/M</td>
<td>None</td>
<td>3/85–8/85 (6.5 mos)</td>
<td>NR 9/85; 1:400 (6 mos) 11/86; 1:600 (4 mos) 13/86; 1:38,400</td>
<td>—</td>
<td>Transient response to splenectomy 8/85; restart rIFN-$\alpha2a$ 2/88–4/88; PR on DCF</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>34/M</td>
<td>None</td>
<td>12/85–12/86 (12 mos)</td>
<td>PR (5/86) 4/86; 1:600 (6 mos) 5/86; 1:2400 6/86; 1:1600</td>
<td>12/86: 12 mos from start of rIFN-$\alpha2a$</td>
<td>DCF</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>63/M</td>
<td>1981, splenectomy 1985, leukeran (2 yrs) 3/85–3/87 (2 yrs)</td>
<td>PR (10/85) 7/86; 1:600 (16 mos) 10/88; Neg</td>
<td>4/87: 0.5 mos from completion of rIFN-$\alpha2a$</td>
<td>Stable, back on rIFN-$\alpha2a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>62/M</td>
<td>8/85, prednisone (3x mos) 8/85–8/87 (2 yrs)</td>
<td>PR (12/85) 6/86; 1:200 (10 mos) 11/87; Neg</td>
<td>12/88: 16 mos from completion of rIFN-$\alpha2a$</td>
<td>Stable, back on rIFN-$\alpha2a$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients had negative pretreatment titers.

Abbreviations: NR, nonresponder; ND, not done; DCF, 2'-deoxycoformycin; Neg, negative.

*Parentheses indicate time from start of rIFN-$\alpha2a$ to date of first positive titer.
after completing 2 years of rIFN-α2a was associated with an increased risk of disease progression.

**DISCUSSION**

The overall incidence of response on this study (80%) compares favorably with that reported by other large groups. Most patients in our study achieved a PR, and no patient achieved a CR. This is in general agreement with a large study published by Golomb et al. In this instance, rIFN-α2b was given at a dose of $2 \times 10^6$ units/m$^2$ subcutaneously (SC) three times per week for either 12 or 18 months. While approximately 15% of patients achieved a CR (and 77% a PR), the authors emphasize that a CR marrow remains abnormal with small numbers (<5%) of persistent hairy cells and increased reticulin. Quesada et al., however, report a complete absence of hairy cells in 9 of 30 patients (30%) treated with rIFN-α2a using a dose and induction schedule identical to ours. Table 5 summarizes the results from these three large studies, as well as our own.

Our study was unable to define any pretreatment variable(s) that could be associated with a high probability of achieving a PR. Specifically, none of the variables analyzed, including prior treatment history, splenectomy, initial WBC count, hemoglobin, platelet count, and percent hairy cells in the initial bone marrow, predicted response. However, Golomb et al. have reported that splenectomized patients appear to have a higher response rate to rIFN-α2b than do patients who have spleens in place at time of treatment. In that study, 96 of 115 splenectomized patients (83%) achieved either a complete or partial response compared with 8 of 13 nonsplenectomized patients (62%). While Quesada et al did not perform a statistical analysis of their study, they did report that five of seven previously untreated patients achieved a CR with rIFN-α2a.

Four patients failed to respond to rIFN-α2a, two patients achieved a response but then progressed while on treatment, and two additional patients died early in the course of therapy. This overall failure rate (23%) is higher than that reported by others. Quesada et al., for example, used rIFN-α2a at the same dose and schedule as the one reported here but state that no patient in their group of 30 failed to respond to treatment. Ratin et al. report a 9% failure rate in a group of 69 patients using rIFN-α2b, and Thompson et al. report a 5% primary treatment failure using the same preparation and treatment schedule as Ratin.

As noted above, no specific clinical characteristics could be identified among the patients who failed early in the treatment program. It is unlikely that poor pretreatment performance status contributed to the high failure rate in our study.

**Table 5. Summary of Published Studies Reporting Long-Term Follow-Up on HCL Patients After Treatment with rIFN-α**

<table>
<thead>
<tr>
<th>Author</th>
<th>rIFN Preparation</th>
<th>Induction Schedule</th>
<th>Maintenance Schedule</th>
<th>Total Length of Rx</th>
<th>No. of Rx Eval</th>
<th>PR (% of Rx)</th>
<th>Median Time to Disease Free Survival at 2 Yrs (%</th>
<th>Disease-Free Survival at 2 Yrs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratin*</td>
<td>rIFN-α2b†</td>
<td>$2 \times 10^6$ U/m$^2$ SC three times/wk for 12 mos</td>
<td>—</td>
<td>12 mos</td>
<td>69/80</td>
<td>13</td>
<td>82</td>
<td>60 (2.5-41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golomb†</td>
<td>Same</td>
<td>Same</td>
<td>2 $\times 10^6$ U/m$^2$ SC three times/wk for an additional 6 mos</td>
<td>18 mos</td>
<td>40/28</td>
<td>15</td>
<td>74</td>
<td>10 (2-19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quesada§</td>
<td>rIFN-α2a</td>
<td>$3 \times 10^6$ U IM three times/wk for an additional 6 mos</td>
<td>12 mos</td>
<td>30/25</td>
<td>30</td>
<td>57</td>
<td>13</td>
<td>5 (3-10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berman</td>
<td>Same</td>
<td>Same</td>
<td>3 $\times 10^6$ U IM three times/wk for an additional 18 mos</td>
<td>24 mos</td>
<td>35/23</td>
<td>0</td>
<td>69</td>
<td>11 (5.5-25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviation: NS, not stated.

*Results published from a single institution study.
†Results published from a multi-institution study. Ninety patients were entered on this protocol and data were reported on 82. Of these, 40 were randomized to receive 18 mos. of treatment, and 42 were randomized to stop therapy after 1 year. The results shown here are from the group randomized to 18 mos. of treatment. Data were reported on 28 of these 40 patients randomized to 18 mos. of treatment.
‡Shering preparation (Intron-A).
§Hoffman-LaRoche preparation (Roferon-A).
¶Calculated total dose assuming average body surface area of 1.7 m$^2$.
##Estimated median time to disease progression based on the assumption that all patients will progress.
Only one of the 35 patients was critically ill at the start of treatment: this was a 33-year-old man with disseminated *M. avium intracellulare*. In contrast to the report by Maziarz et al., treatment with rIFN-α2b did not halt progression of his infection and he expired within 2 weeks of starting therapy.

One possible explanation for this relatively high failure rate is the incidence of neutralizing antibody formation. This is a complex issue, however, as route of administration, sampling time relative to drug administration, differences in interferon preparation, and the assay method used have all been implicated in the percentage of positive antibody titers reported. In our study, neutralizing antibodies to rIFN-α2a were detected in 6 of 32 patients studied (19%), which is similar to the incidence reported by Steis et al. In their review, 16 of 51 patients (31%) treated with rIFN-α2a with an induction schedule similar to ours developed neutralizing antibodies. However, only 6 of 16 patients (31%) in their study manifested clinical resistance to rIFN-α2a, while in our study, all patients demonstrated some form of resistance to therapy: three patients were primary nonresponders, one patient achieved a PR but then progressed, and two patients relapsed after completing the 2-year treatment course (Table 3). It is, nonetheless, important to note that nine patients who were antibody negative also relapsed after therapy was discontinued.

The incidence of neutralizing antibody development in patients who have received rIFN-α2b for HCL is not clearly established. Spiegel et al. initially reported that none of 75 patients tested using the immunoradiometric assay for antibody detection had positive titers; however, subsequent comparison by Itri et al. of this method and the solid-phase enzyme immunoassay as used in this study has demonstrated that the immunoradiometric assay is less sensitive. In the Itri study, 48 of 100 samples that had tested positive in both the solid-phase immunoassay and the interferon anti-viral neutralization assay tested negative in the immunoradiometric assay. More recently, Spiegel et al. have reported that samples tested using both the enzyme immunoassay and the viral neutralization assay were found to have a very low incidence of antibody formation.

Nonetheless, clinically meaningful titers have been reported in patients who have received rIFN-α2b for other malignancies. Freund et al. found antibody titres in 8 of 27 patients with chronic myelogenous leukemia treated with rIFN-α2b at a dose of $5 \times 10^6$ units subcutaneously three times per week; all eight patients either relapsed or proved to have refractory disease. Similarly, Oberg et al. report that 3 of 20 patients with carcinoid tumors treated with rIFN-α2b at a mean dose of $6 \times 10^6$ units subcutaneously three times per week developed positive titers; two of these patients lost their initial response and one patient had progressive disease despite treatment. Thus, while it may be difficult to compare the incidence of neutralizing antibody formation with each rIFN-α preparation given the differences in dose, schedule, timepoints of measurement, and technical assay variations, the significance of a positive antibody titer appears to be the same; ie, these patients may not respond to therapy with rIFN-α or be at high risk for relapse.

The wide variations in antibody titer observed in this study are similar to those reported by Steis et al. In that study, one patient's titer fluctuated threefold while on a three times per week injection schedule, and another had a progressive drop in titer on an increasing dose schedule. It is not clear why such variations occur. As noted, sampling time after rIFN-α2a injection may affect the titer and, in the absence of specific collection time points, may be responsible for the variations noted in these two studies.

The median time to progression of disease among our group of 11 patients was 10 months and is similar to that reported by Golomb et al. and Quesada et al., which were 6.5 and 6 months, respectively (Table 5). Ratain et al. used a Kaplan-Meier plot to calculate the median time to relapse among their entire group of patients. This median, 25.4 months, is based on the assumption that all patients will eventually relapse and therefore cannot be directly compared with the other relapse rates.

Based on the results in the three previously published papers and the data presented in this current study, some preliminary observations can be made. First, the majority of patients achieve a PR that appears to be independent of rIFN-α preparation, schedule administration, or total dose given. Second, half of the patients who relapse will do so within 1 year of completion of therapy. This does not appear to be related to the rIFN-α preparation or the schedule of administration. Third, while the disease free survival after 2 years of treatment on our protocol is shorter than that reported after 1 year of rIFN-α2b, it should not necessarily be concluded that longer periods of treatment are less beneficial. Rather, one can conclude that additional therapy with rIFN-α2a beyond 1 year does not appear to prolong response duration. In this regard, it will be important to evaluate the long-term results of Quesada et al.'s 1 year study using rIFN-α2a and Golomb et al.'s 18 month study using rIFN-α2b.

It is also apparent from Table 5 that a subset of patients will have a long-term remission after 12, 18, or 24 months of therapy. In an attempt to identify patients at high risk for relapse after completing 2 years of rIFN-α2a, we performed a multivariate analysis analyzing six posttreatment variables. We recognize that our study is limited given its relatively small number of patients; nonetheless, the Cox proportional hazards regression analysis suggested that a low platelet count at the end of 2 years of treatment was associated with a high relapse rate (Fig 3). In a similar type of analysis, Ratain et al. demonstrated that the percent of residual hairy cell leukemia in the bone marrow after treatment and a high neutrophil acid phosphatase (NAP) score were important variables for relapse.

It is of interest to note that in this study, despite its 2-year treatment course, no patient developed a chronic fatigue...
syndrome as reported by Golomb et al using rIFN-α2b. The reasons for this remain uncertain. It is possible that the structural differences between the two preparations are important in this regard; alternatively, the initial induction period of daily injections versus three times per week may facilitate tachyphylaxis.

It is clear that further follow-up of these long-term studies is needed before final conclusions can be made concerning the optimal treatment schedule of rIFN-α for patients with HCL. Nonetheless, we would suggest that all patients be carefully evaluated after completion of their original therapy program and that those who have poor prognostic features as described either in this study or that of Ratain et al be continued on therapy for longer periods of time, perhaps indefinitely. Patients who are not at high risk for disease progression may be taken off their prescribed course of treatment until more is known about long term, ie, 5 to 10 year follow-up, of this group. We also suggest that antibody titers be determined on all patients receiving rIFN-α2a, as both this study and that of Steis et al suggest that patients who develop positive titers are at high risk of either primary failure or relapse.

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