Very Low Dose α-2b Interferon for the Treatment of Hairy Cell Leukemia

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α-2b interferon (α-2b IFN), administered at 2 × 10^6 U/m^2 three times per week is highly effective in the treatment of progressive hairy cell leukemia (HCL) and in the retreatment of patients who have relapsed after previous IFN therapy. To determine if a lower interferon dose would induce a comparable antileukemic effect with less toxicity, α-2b IFN was administered at 2 × 10^6 U/m^2 subcutaneously three times per week to 17 patients with progressive HCL. Thirteen patients had HCL in relapse after a previous response to α-2b IFN; four patients were previously untreated. The median duration of treatment was 9 months. Toxicity consisted only of transient, mild flu-like symptoms in two patients. Of the 13 previously IFN-treated patients, four had a minimal response, one had no response, and eight had progressive disease. Of four previously untreated patients, one had a partial response, two had a minimal response, and one had no response. In seven of eight patients whose disease progressed on low-dose IFN, the dose was escalated to 2 × 10^6 U/m^2 three times per week, and all seven patients demonstrated hematologic response within 3 months to the dose escalation. We conclude that α-2b IFN at 2 × 10^6 U/m^2 three times per week is relatively ineffective for the treatment of relapse after previous IFN therapy.

The dose and schedule of administration of α-2b IFN were selected empirically, based upon clinical results obtained with partially purified leukocyte interferon. Little is known about the dose-response relationship of alpha interferon in the treatment of HCL. Preliminary results with nonrecombinant leukocyte interferon (Welferon) suggested that a low dose was as effective as a higher dose against progressive HCL. The current trial of recombinant α-2b IFN was initiated to determine whether a very low-dose regimen (one tenth the "standard") would improve the therapeutic ratio by inducing a high response rate but with less toxicity.

MATERIALS AND METHODS

Seventeen patients with progressive HCL, manifested by anemia (Hgb <8 g/dL), neutropenia (<1,000 cells/μL), thrombocytopenia (<100,000 cells/μL) and/or rapidly progressive leukemic phase were entered in a phase IV study of α-2b IFN administered at 2 × 10^6 U/m^2 SC three times per week (Table I). One patient (patient no. 1) required an escalation of interferon dosage after 3 months because of rapidly progressive HCL; the other patients were treated for 6 to 12 months. Four patients were previously untreated; the remainder of the patients had previously responded to treatment with α-2b IFN at 2 × 10^6 U/m^2/d for 12 to 18 months, but had developed progressive HCL 6 to 36 months after discontinuing therapy.

The protocol was approved by the Human Subjects Review Committee of the University of Washington, and all subjects gave consent.

The α-2b IFN (Schering Corp, Kenilworth, NJ) was obtained as a lyophilized powder (5 × 10^6 IU per vial), and was reconstituted with sterile saline and self-administered SC. After the completion of their initial IFN treatment, and none were positive. Serum samples were obtained immediately before, and at the completion of the current protocol to test for serum antibody. The protocol was approved by the Human Subjects Review Committee of the University of Washington, and all patients gave informed consent.

RESULTS

Toxicity was observed in only two of 17 patients and consisted solely of mild, transient flu-like symptoms during the first week of therapy. The clinical response of all patients...
One patient (patient no. 10) developed neutralizing antibody. The current study, which escalates the dose of IFN, and continues to respond after 6 months despite the persistence of neutralizing antibody.

is summarized in Table 1. Of the 13 patients previously treated with IFN, four had a minor response, one had no response, and eight had progressive disease on the current regimen. Before treatment, the median percentage infiltration of the marrow by hairy cells in these 13 patients was 60% (range, 5% to 90%), but the marrow involvement increased to 80% (range, 20% to 98%) at the completion of the current protocol. Of the four patients not previously treated with IFN, one had a partial response, two had a minor response, and one had no response. In these four patients, the median marrow infiltration by hairy cells decreased from 60% (range, 10% to 80%) to 10% (range, 5% to 30%) posttreatment.

The results of the current trial, however, indicate that for HCL patients relapsing after previously successful a-2b IFN therapy, very low dose a-2b IFN is relatively ineffective for the induction of a second remission. Furthermore, of ten patients who relapsed after discontinuing therapy with 2 × 10^6 U/m^2, ten responded to retreatment by the same regimen.

It was hypothesized that a better therapeutic ratio might be achieved with a dose far lower than 2 × 10^6 U/m^2, as suggested by preliminary results reported with Welferon. The optimal dose of alpha interferon for a maximal antileukemic effect with minimal toxicity has not yet been determined. A large, multicenter trial of recombinant a-2b IFN administered at 2 × 10^6 U/m^2 three times per week to over 200 patients documented a response rate of 88%. In the rare patients who did not respond to this dose, escalation of the dose to 10 × 10^6 U/m^2 did not induce responses and was associated with increased toxicity. Furthermore, of ten patients who relapsed after discontinuing therapy with 2 × 10^6 U/m^2, ten responded to retreatment by the same regimen.2

In the results of the current trial, however, indicate that for HCL patients relapsing after previously successful a-2b IFN therapy, very low dose a-2b IFN is relatively ineffective for the induction of a second remission. Furthermore, the clinical course in patients no. 1, 2, 10, and 12 suggests a significant dose-response relationship to the antileukemic effect of a-2b IFN. In patient no. 2, for example, despite a 9-month trial of very low-dose a-2b IFN, the HCL progressed. However, within 3 months of treatment with the escalated dose of 2 × 10^6 U/m^2, there was significant improvement in peripheral blood counts. It is unlikely that serum antibodies to interferon are responsible for the low response rate, as only one patient was found to have detectable neutralizing antibody. The current study, which
involved only four previously untreated patients, does not permit firm conclusions about the responsiveness of these patients to very low-dose IFN. Although significant reductions in marrow infiltration by hairy cells were achieved, the clinical responses observed in these patients seem to be inferior to those reported in larger series using \(2 \times 10^5\) U/m\(^2\) \(\alpha\)-2b IFN (approximately 80% complete plus partial response rate).\(^1\)

In conclusion, for HCL patients with progressive diseases after previous response to \(\alpha\)-interferon, a very low-dose regimen of \(\alpha\)-2b IFN at \(2 \times 10^5\) U/m\(^2\) three times per week is ineffective, and the use of this regimen in an attempt to minimize toxicity may prolong the duration of dangerous cytopenias. Until future clinical trials identify the optimal \(\alpha\)-2b IFN dosage for HCL, \(2 \times 10^6\) U/m\(^2\) three times per week remains the recommended treatment regimen for patients who relapse after previous interferon therapy. Given the negligible toxicity associated with very low dose \(\alpha\)-2b IFN, the use of this regimen for the maintenance of remission in HCL should still be investigated.

REFERENCES


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[see comments]

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