A New Treatment for Polycythemia Vera: Recombinant Interferon alfa

By Richard T. Silver

Recombinant interferon alfa, a natural product with growth inhibitory capabilities, has been demonstrated for the first time to have significant therapeutic efficacy in controlling the red cell mass in patients with the myeloproliferative disease polycythemia vera. The starting dose was $3.0 \times 10^6$ U three times a week, subcutaneously (SC). In three patients the dose required was $5.0 \times 10^6$ U five times a week, SC. Side effects were easily tolerated. The striking advantage in the use of this drug is its presumed absence of antileukemic effect. Further evaluation is necessary, but the initial responses are encouraging.

POLYCYTHEMIA VERA is a disease of long duration and varied complications in which several species of hematopoietic cells are involved simultaneously or sequentially in the proliferative process. Although most hematologists believe that survival is increased and complications are reduced in treated as compared with untreated patients, conflicting opinions regarding optimum therapy are still held by various investigators. Phlebotomy alone as the sole form of therapy is advocated by those who believe that the major causes of morbidity and mortality in polycythemia vera will be prevented by correcting the increased red cell mass and blood volume. However, phlebotomy has its risks in the elderly patient and may produce thrombocytosis leading to thrombosis. Others endorse myelosuppressive therapy, citing the additional beneficial effects of these agents on thrombocytosis, leukocytosis, hyperuricemia, and hepatosplenomegaly. Unfortunately and importantly, these drugs may be leukemogenic.

Because of the slow but, nevertheless, progressive nature of polycythemia vera (even in patients treated with phlebotomy only) and in an attempt to avoid the leukemogenic effects of either $P_3$ or chemotherapy (particularly in younger individuals), alternative treatment modalities have been constantly sought. Recombinant interferon alfa (rIFNa) is a biologic response modifier. It has had demonstrated myelosuppressive activity that has been used in the treatment of chronic myeloid leukemia by others and others. It has had demonstrated effectiveness in treating elevated platelet counts in patients with chronic myeloid leukemia, polycythemia vera, and essential thrombocytosis. Platelet-derived growth factor (PDGF) initiates proliferation of fibroblasts. Recent studies by Lin et al indicate that interferon alfa antagonizes the action of PDGF by interfering with the activation of G0 cells for G1 traverse and S phase entry. The important clinical implication of these observations is that interferon alfa may control the proliferative aspects of polycythemia vera and inhibit the development of myelofibrosis, a consequence of the natural history of the disease. The fact that interferon alfa is not leukemogenic adds significant attraction to its proposed use.

The effectiveness of rIFNa was briefly noted after the successful treatment of three patients with polycythemia vera. In this report, follow-up of the first three patients is extended to approximately 3 years, and two additional patients have been included.

RESULTS

After receiving written informed consent, five patients previously treated with phlebotomies only for control of their disease were treated with rIFNa. The age, sex, year of diagnosis, and average number of phlebotomies per year before the institution of rIFNa for each patient are shown in Table 1. There were three women and two men whose ages ranged from 46 to 64 years. Although the duration of the disease differed, the activity of the disease was essentially the same for four patients, since the numbers of phlebotomies per year were nearly the same (Table 1). The fifth patient required 12 phlebotomies in the 5 months before the initiation of rIFNa.

Values of the red blood cell, white blood cell, and platelet counts, hematocrit, and spleen size at diagnosis and median counts during phlebotomy and 1 year after rIFNa are shown in Table 2.

The starting dose was $3.0 \times 10^6$ U three times per week, SC. Since good control of disease occurred in two patients, it was possible after 4 months to reduce gradually the dose of rIFNa to $1.0 \times 10^6$ U and then to $0.45 \times 10^6$ U three times per week, and, finally, to discontinue it after 2 months. In both patients, the hematocrit slowly rose, and rIFNa was re-started after 4 months and maintained at a dose of $0.5 \times 10^6$ U twice a week. In the next three patients, the starting dose of $3.0 \times 10^6$ U three times per week was inadequate; it was subsequently escalated to $5.0 \times 10^6$ U five times per week, and remission was induced within 4 months. After the hematocrit fell to 45.0% or lower, the maintenance dose was $5.0 \times 10^6$ U three times per week. Patient 3 required phlebotomies during the first 6 months after rIFNa was started (Table 1). His dose has remained at $5.0 \times 10^6$ U, three times per week. Patient 4...
required one phlebotomy during the first 3 months of rIFNa therapy. Of considerable interest is the fact that the spleen regressed in size in four patients after rIFNa whereas it had remained the same or enlarged slightly during treatment with phlebotomy. In the fifth patient (Patient 2) the spleen remained unchanged in size. This was related to a previous documented portal vein thrombosis.

The side effects of rIFNa were similar to those reported in other studies and were dose-related. These included myalgia, low grade fever, and muscle weakness in three of the five patients. Virtually all symptoms were relieved with acetaminophen in the usual dose. One patient complained of dry skin.

Interval bone marrow determinations 1 year after the institution of rIFNa indicate that the marrows have remained hypercellular with no significant change compared with pretreatment marrows. There has been no change in marrow reticulin or levels of serum erythropoietin.

**COMMENTS**

For the first time, these results clearly demonstrate the effectiveness of rIFNa in controlling the excess red cell mass in polycythemia vera. Red cell values were controlled within 6 months, eliminating the need for phlebotomy in all five patients. Furthermore, as previously noted in other myeloproliferative diseases, elevated platelet counts were reduced and spleen size diminished after rIFNa. In all patients, it was possible to subsequently maintain the patient on relatively small doses of drug.

Based on these studies, a reasonable starting dose is 3 to 5 x 10^6 units SC, three to five times per week. It is possible that subsequent patients may require more or less interferon, depending upon response. Obviously, further follow-up is required to determine the development, frequency, and type of complications that may occur with long-term use of rIFNa. The occurrence of acute leukemia, myelofibrosis, and cytogenetic abnormalities will be monitored carefully. In the meantime, further evaluation of this drug in a larger number of patients with this disease is certainly warranted.

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**REFERENCES**

A new treatment for polycythemia vera: recombinant interferon alfa [see comments]

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