

Treatment of Polycythemia Vera with Recombinant Interferon

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Polycythemia vera (PV), a myeloproliferative disease, is characterized by an increased red cell mass and throm-bohemorrhagic complications. In general, treatment has consisted of phlebotomy to reduce the red cell mass. However, because only treating with phlebotomy is associated with early, frequently fatal thrombosis or, hemorrhage, myelosuppressive therapy is also used. The agents used in the past, chlorambucil and radioactive phosphorus, are leukemogenic [1]. Although hydroxyurea (HU) is used as an alternative drug because of effectiveness and convenience, a potential for leukemia still exists [2,3], especially in patients who develop postpolycythemic myeloid metaplasia [4-6]. Moreover, despite conventional treatment with phlebotomy and HU, many patients experience night sweats and pruritis and also develop iron deficiency. The inexorable course of polycythemia vera includes progressive splenomegaly and myelofibrosis, even in those patients treated with myelosuppressive therapy. For all these reasons, other treatments are still required.

Interferon alfa (IFN α) has broad effects on the hematopoietic system. IFN inhibits erythroid progenitors [8] and erythroid burst-forming units in vitro [9] and produces morphologic and biochemical changes in megakaryocytes [10], including a decrease in megakaryocyte density and size, presumably affecting megakaryocyte maturation and platelet release. In PV, biochemical abnormalities of platelets characterized by impaired conversion of exogenous arachidonic acid by platelet thromboxane b₂ and correction of that deficiency by IFN α has been reported [11]. The use of rIFN α also antagonizes platelet-derived growth factor (PDGF) [12]. This is important because PDGF plays a major role in the pathogenesis of myelofibrosis [13]. When compared with nonspecific myelosuppressive drugs, or PHL-O, rIFN α represents a treatment modality that may fundamentally

alter the course of the disease, and thus offers a physiologic basis for its use in PV.

After the initial reports of the beneficial results of IFN α in patients who have PV [7,14], others confirmed its value [15]. When reports of reduction in red blood cell and platelet counts and spleen size were uniformly observed, accompanied by a decrease in constitutional symptoms, especially pruritis. Although PV is now treated in the United States and abroad with rIFN α more frequently, most series have been small in number, and reports of the long-term effects and tolerance of rIFN α are limited.

I report therefore, the use of rIFN α in 55 patients with PV; treated at our institution over the past 15 years.

All patients were initially phlebotomized to a hematocrit (HCT) between 40% and 45% and started on rIFN α 1,000,000 units (1 MU) tiw sc escalating to 3 MU tiw sc with upward or downward modification of the dose as necessary, and as tolerated. Complete clinical response (CCR) was defined as a PHL-free HCT of 40-44%, and platelets 600,000/ml. There were 28 men and 27 women, with an average age of 49 years, and half were under the age of 50. The median disease duration by quartiles prior to rIFN α ranged from 33 to 205 months, the longest 356 months. Previous therapy with HU did not affect the subsequent response to rIFN α . Prior to rIFN α the number of phlebotomies per year ranged from 3 to 70 with a median of 11. The median duration of rIFN α therapy by quartiles ranged from 12 to 101 mos, the longest 163 mos. After 1 year, all pts had a CCR, but subsequently 4 pts required 1 to 2 PHL/year to maintain CCR. The long-term maintenance dose of rIFN α averaged 2-3 MU tiw sc. Annual marrow examination indicated persistent hypercellularity.

Therapy has been discontinued in 15 pts, all over the

age of 55. Three patients entered and sustained remission, one lacked sufficient insurance coverage, one developed a large cell lymphoma (treated successfully with cyclophosphamide, adriamycin, vincristine, prednisone (CHOP) with both lymphoma and PV in sustained remission) and ten due to toxicity. Of these ten, seven had the familiar constitutional symptoms secondary to rIFN α , which were not acceptable to the pts even at a low dose of rIFN α . One developed severe dermatitis, one sustained complex seizures and one had peripheral neuritis. These pts have been subsequently treated with hydroxyurea (HU), anagrelide, or both, without difficulty. While on rIFN α , three patients developed myelofibrosis characterized by a small spleen and modest marrow fibrosis, 18, 25 and 30 years after the initial dose of PV. Two of these pts have required HU and one prednisone as supplemental therapy to rIFN α . No pt in this series has developed leukemia or any thromboembolic phenomena, the latter reflecting the modern overall care of the PV pt.

I conclude that rIFN α is an effective agent, with an acceptable degree of toxicity, for treating PV, particularly in young pts, for long periods of time.

References

1. Berk PD, Goldberg JD, Donovan PB, et al. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. *Semin Hematol.* 1986;23:132-143.
2. Weinfeld A, Swolin B, Westin J. Acute leukemia after hydroxyurea therapy in polycythemia vera and allied disorders: Prospective study of efficacy and leukaemogenicity with therapeutic amplications. *Wur Haematol.* 1994;52:134-139.
3. Silver RT. Hydroxyurea and sickle cell crisis [letter]. *N Engl J Med.* 1995;333:1008.
4. NA jean Y, Deschamps A, Driesch C, et al. Acute leukemia and myelodysplasia in polycythemia vera. *Cancer.* 1988;61:89-95.
5. NA jean Y, Driesch C, Rain JD. The very long-term course of polycythemia: A complement to the previously published data of the Polycythemia Vera Study Group. *Br J Haematol.* 1994;86:233-235.
6. Na jean Y, Mugnier P, Driesch C, et al. Polycythemia vera in young people: An analyses of 58 cases diagnosed before 40 years. *Br J Hematol.* 1987;67:285-291.
7. Silver RT. A new treatment for polycythemia vera: Recombinant interferon alfa. *Blood.* 1990;76:664-665.
8. Means RT, Krantz 58. Inhibition of human erythroid colony-form units (CFU-E) by interferons: Different modes of action for alpha, beta and gamma interferons. *Blood.* 1991;78:1215 (306a).
9. Costello R, Lerza A, Cerruti D, et al. The in vitro and in vivo (effect of recombinant interferon 0-20 on circulating haemopoietic progenitors in polycythaemia vera. *Br J Haematol.* 1994;87:621-623.
10. Chott A, Gisslinger H, Thiele J, et al. Interferon-alpha induced morphological changes in megakaryocytes: A histomorphological study on bone marrow biopsies in chronic myeloproliferative disorders with excess thrombocytoses. *Br Haematol.* 1990;74:10-16.
11. Sinzinger H, Linkesch W, Ludwig H, et al. Impaired conversion of exogenous arachidonic and by platelets to thromboxane b2 and correction of that deficiency by interferon-alpha. *Prostaglandins.* 1990;40:351-360.
12. Lin SL, Kikuchi T, Pledger WJ, et al. Interferon inhibits the establishment of competence in Go/S phase-transition. *Science.* 1986;233:356-359.
13. Martyre MC, Nagdelenat H, Caldo F. Interferon gamma in vivo reverses the increased platelet levels of platelet-derived growth factors in transforming growth factor-b in patients with myelofibrosis with myeloid metaplasia. *Br J Haematol.* 1991;77:431-435.
14. Silver RT. Interferon- α 2b: A new treatment for polycythemia vera. *Ann Int Med.* 1993;119:1091-1092.
15. Thomas DJ, Marshall J, Russel RW, et al. Cerebral blood-flow in polycythaemia. *Lancet.* 1977;2:161-163.