A prospective comparison between treatment with phlebotomy alone and with interferon-alpha in patients with polycythemia vera

Summary

Interferon alpha (α-IFN) is increasingly used for the treatment of patients affected by polycythemia vera (PV). As prior studies are difficult to interpret in view of the lack of appropriate controls, we undertook a randomized comparison of lymphoblastoid α-IFN (α n-1 IFN) treatment against venesection treatment alone. In a crossover trial, we treated 22 PV patients alternatively for 5 months each with 3 MU/day sc of α n-1 IFN and phlebotomy alone. During IFN treatment, red blood cell count and hematocrit level were well controlled in both trial groups, reducing or eliminating the need for phlebotomy in all patients; furthermore, platelet number and white blood cell count declined during α-IFN therapy. In addition, the number of symptomatic patients was greatly reduced, and in six patients a reduction in splenic size was observed. Finally, the only patient with chromosomal abnormalities showed a complete cytogenetic conversion after 5 months of α-IFN therapy. Thus, for the first time, our results provide the unequivocal demonstration that α-IFN is superior to phlebotomy in controlling the pathologic expansion of erythroid elements and all the clinical aspects of this disease.

Key words

α-IFN · Phlebotomy · Polycythemia vera

Introduction

Polycythemia vera (PV) is a clonal disorder of the hematopoietic stem cell with unregulated expansion of the erythroid, myeloid, and megakaryocytic cell lineages. Proof of clonality has been established by cytogenetic means [7], by electrophoretic analysis of the X-encoded G6PD isoenzymes [15], by the different relative utilization of 2-αG6P [6], and by X-linked DNA polymorphisms [20]. Thrombosis and, less frequently, hemorrhage are the most important clinical complications and the major causes of morbidity and mortality [1]. About 10–20% of the patients progress to “spent phase”, a stage characterized by marrow fibrosis with extramedullary hematopoiesis and pancytopenia [5]. About 2–15% of patients develop acute myeloid leukemia (AML) of various French-American-British (FAB) subtypes. Acute leukemic transformation forms a part of the natural history of PV but is more frequent after treatment with alkylating agents and radioactive phosphorus [5, 10]. For this reason, hydroxyurea (HU) has tended to be employed. In association with phlebotomy, HU proved able to reduce the risk of thrombosis. However, some authors [16, 21, 23, 24] have reported cases of acute leukemia following treatment with HU in patients with ET, and the analysis of 48 PV patients by Nand et al. [12] revealed that any myelosuppressive treatment, including HU, is associated with an increased incidence of acute leukemia. The results of Nand et al. confirm doubts previously advanced by Donovan et al. in 1984 [4] regarding the mutagenic potential of HU. Theoretical considerations have raised similar doubts [18]. Furthermore, a case of non-Hodgkin’s lymphoma developing in a PV patient treated only with phlebotomy and HU was recently described [8]. To date, there is thus no generally accepted treatment for PV which both reduces the risk of thromboembolism and does not increase the frequency of secondary myel-
ofibrosis and terminal blast transformation. Consequently, a nonleukemogenic, and nongonadotoxic drug needs to be developed which is able to exert not only a "cosmetic" effect but also a fundamental influence on PV. This drug could be α-IFN. Recent reports indicate that in PV patients interferon-alpha (α-IFN) is able to induce and maintain complete hematological remission [2, 3, 13, 19, 22]. On the basis of these findings, we undertook a prospective study of α-IFN in PV patients. As prior studies with IFN are difficult to interpret in view of the lack of appropriate controls, this protocol was designed to prospectively compare treatment with α-IFN with treatment by phlebotomy alone.

Materials and methods

Patients

As of January 1992, 22 evaluable PV patients from five Italian university hospitals had entered the study after giving informed oral or written consent, depending on local ethical committee rules. The diagnostic criteria were those of the Polycythemia Vera Study Group. The patients (13 men and nine women; average age 56.5 years, range 27–70) were newly diagnosed (n = 11) or had been previously treated (n = 11) for a maximum of 1 year with phlebotomy alone (n = 4), pipobroman alone (n = 1), or both treatments (n = 6). Pipobroman treatment was suspended at least 3 months before patients entered the study. On entry to the protocol, 14 patients (63.6%) had symptoms related to erythrocytosis/thrombocytosis; these included: pruritus (n = 9), acroparesthesias (n = 7), acrocyanosis (n = 5), peripheral vascular ischemia (n = 1), enterorrhagia (n = 1), and dizziness (n = 1). Six newly diagnosed patients had a prior history of related symptoms 6–10 months before initiation.

Plan treatment

This study was designed to verify the ability of lymphoblastoid α-IFN (α n-1 IFN) (Wellferon, Wellcome, Italy) to control the myeloproliferative process in PV patients. We chose a crossover study in which patients receive two treatments in sequence, because this method can produce results that are statistically and clinically valid with far fewer patients than would be required in a parallel study. After 2 months of treatment with phlebotomy alone to obtain and stabilize hematocrit at ≤45%, patients were randomly divided into two treatment groups: 1. Patients enrolled in group A were treated with α n-1 IFN administered subcutaneously at a dose of 3 MU daily for 5 months. During this period, patients showing Ht > 45% were treated with venesection. After a 2-month wash-out to avoid carry-over effects, patients were observed for 5 months and treated with phlebotomy alone to maintain Ht below 45%.

2. Patients enrolled in group B were first observed for 5 months and treated with venesection alone when Ht > 45%. For the next 5 months, they were treated with α n-1 IFN 3 MU/daily sc. Patients showing Ht > 45% during this period also received phlebotomy. Ordinarily, the volume of each venesection was 500 ml of blood. After initial treatment by hospital staff, IFN injections were administered by the patients themselves on an outpatient basis. Any flare symptoms that appeared were treated with paracetamol.

Inclusion and exclusion criteria

Inclusion criteria were a rigorous diagnosis based on the PVSG criteria. Exclusion criteria were: (a) age over 70 years, (b) any associated diseases which could prevent treatment, and (c) patient’s refusal.

Evaluation

Patient assessment included: a physical examination, urine test, blood counts, evaluation of liver and renal functions, coagulation studies, serum iron and total iron-binding capacity, serum ferritin concentration, arterial oxygen saturation, serum B12 concentration, red cell mass, bone marrow aspiration and biopsy, cytogenetic analysis, and spleen size, confirmed by ecography. After an initial evaluation in the hospital, patients were followed up on an outpatient basis. Blood counts, physical examination, and partial evaluation of liver and renal function were done every 2 weeks, while serum iron, iron-binding capacity, and serum ferritin concentration were determined only at the beginning and at the end of both treatment periods. Bone marrow aspiration and biopsy and spleen size measured by ecography were also taken at the end of 5 months’ IFN therapy.

Statistics

All data were processed with the 2V program of the BMDP software. Statistical calculations were performed using the analysis of variance (ANOVA) for crossover design. Assumptions of validity were examined after ensuring that the unit/treatment additivity and the treatment effect were the same in both periods.

Results

Although the duration of the disease and previous therapy differed, the PV activity was essentially the same in both groups of patients, as phlebotomy requirements during the 2 months before randomization were almost equal (55 and 54 phlebotomies for group A and group B, respectively). Of the 22 patients, one enrolled in group A was not evaluable because IFN treatment was discontinued after 1 month, in accordance with the patient’s wishes, although there was no evidence of adverse side effects. In groups A and B, the ANOVA analysis of the number of phlebotomies, WBC, and platelet counts (Figs. 1, 2) showed a significant increase from the α-IFN treatment period to the period of phlebotomy alone, while the MCV showed a significant increase from the phlebotomy-alone period to the α-IFN treatment period (Fig. 2c). During α-IFN treatment, serum iron (SI), and serum ferritin concentrations (SFC) tended to increase in both groups, while they fell during the period of venesection alone (F1,19 = 15.9, p = 0.008 and F1,19 = 12.19, p = 0.024, respectively). In group A, SI (μg/dl) and SFC (μg/l) increased from 66 and 40 to 68 and 43, respectively; they declined from 70 and 42 to 40 and 13 during venesection alone. In group B, SI and SFC decreased from 81 and 78 to 49 and 38 during venesection alone and increased from 49 and 38 to 57 and 41 during IFN treatment. The spleen, which was enlarged in 14 of 21 patients (66.6%), had decreased in size in six patients (42.8%) after 5 months of α-IFN treatment. Analysis of 21 bone marrow biopsies showed that after IFN treatment the abnormal proliferation of erythroid elements had decreased in 14 patients (66.6%) and was essentially unchanged in the