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Alpha Interferon Treatment of Essential Thrombocythaemia and Other Myeloproliferative Disorders with Excessive Thrombocytosis

Xenophon Yataganas, John Meletis, Eleni Plata, Nora Viniou, Filippos Deligiannis, Christina Tsekoura, Ersi Voscaridou, Viki Boussiotis, John Rombos, Georges Vayopoulos, Christos Kittas and Phaedon Fessas

The effect of recombinant interferon alfa-2b on platelet count, thrombocytosis-associated symptoms and marrow fibrosis was studied in 18 patients with myeloproliferative diseases and associated thrombocytosis (nine with essential thrombocythaemia, three with polycythaemia vera, three with myelofibrosis and three with chronic myelogenous leukaemia). A reduction of the platelet count below 600 x 10⁹/L was achieved in 94%, and below 400 x 10⁹/L in 77% of the patients within 8 to 330 days of treatment. The selective thrombocytosis-reducing effect of alpha interferon was maintained for long periods of time in most patients without serious side effects. Thrombocytosis-associated symptoms were relieved once the number of platelets was reduced to near normal levels. Marrow reticulin content was found to be reduced after treatment in two of the seven patients studied. Side effects of alpha interferon were flu-like symptoms, which usually subsided within 7 days of treatment.
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INTRODUCTION

EXCESSIVE THROMBOCYTOSIS is a common feature of the myeloproliferative diseases (MPD). It contributes to the increased prevalence of thrombotic complications and bleeding [1] and to the development of marrow fibrosis [2]. It may also cause symptoms. With the exception of chronic myelogenous leukaemia (CML), the course of MPD is generally considered to be benign. However, the median survival in patients with polycythaemia vera (PV) and essential thrombocythaemia (ET) is limited, and progression to acute leukaemia has been observed, especially after cytoreductive treatment [3]. Since cytotoxic therapy is leukaemogenic and the usefulness of platelet-aggregation reducing agents is uncertain [4], new modalities of treatment of thrombocytosis in MPD need to be explored.

Alpha interferon has an anti-proliferative effect on human megakaryocytic progenitor cells [5], antagonizes the action of the platelet-derived growth factor (PDGF) on fibroblasts [6] and has been found to induce haematological, and even cytogenetic remission [7], in CML. The present study evaluated the role of alpha interferon in the control of thrombocytosis and its adverse effects in ET and other MPD.

PATIENTS AND METHODS

Eighteen patients with MPD (13 women and five men), aged 31-67 (median 46) years, took part in the study. The diagnoses (according to the criteria of the Polycythemia Vera Study Group) were: ET, nine patients; myelofibrosis (MF), three; PV, three; and CML, three. One patient with CML had relapsed after allogeneic bone marrow transplantation, and the other two had for a short time received hydroxyurea, which had failed to reduce the platelet count. Most patients had minor symptoms that may have been related to thrombocytosis: dizziness (four patients); headache (two); weakness (two); paraesthesia (one); pruritus (one); bruising (one); vascular ischaemia (one). Six patients had no symptoms or clinical signs of the disease. Splenomegaly was found in three patients with ET and five with other MPD.

Bone marrow reticulin was scored [8] before the start of the study and every 6 months thereafter in patients whose platelet count was maintained continuously below 600 x 10⁹/L.

TREATMENT

Recombinant interferon alfa-2b (Schering-Plough, Greece) was administered subcutaneously at a dose of 3 million units (MU) daily for 4 weeks. The dose was increased to 5 MU at day 30 if the platelet count remained above 600 x 10⁹/L. The dose of alpha interferon and frequency of administration were reduced progressively when the platelet counts reached upper normal levels. The objective of maintenance treatment was to administer the lowest effective dose of alpha interferon, usually 3 MU three times a week (t.i.w.). The dose was reduced if side effects occurred, and treatment was discontinued if intolerable side effects did not improve with dose adjustments, if there was evidence of active infection or if thrombocytosis recurred during treatment. All participants gave informed consent to treatment.

The patients learned to self-administer alpha interferon subcutaneously within the first 2 weeks and were managed as

Correspondence to: X. Yataganas.
X. Yataganas is at the University of Athens Medical School, Laikon General Hospital, Athens, 115 27 Greece. J. Meletis, E. Plata, N. Viniou, F. Deligiannis, Ch. Tsekoura, E. Voscaridou, V. Boussiotis, J. Rombos, G. Vayopoulos, Ch. Kittas and Ph. Fessas are at the University of Athens Medical School, Laikon General Hospital, Athens, 115 27 Greece.

out-patients. Clinical, haematological and biochemical assessments were made twice a week initially and every two to three weeks thereafter. Flu-like symptoms were treated with paracetamol.

RESULTS

A reduction of the platelet count below 600 x 10⁹/L and 400 x 10⁹/L was achieved in 17 of 18 (94%) and 14 of 18 (78%) patients at a mean time of 27.5 and 103.7 days, respectively (Table 1). A greater than 50% reduction in the mean platelet count was obtained at day 30 of treatment in patients with ET and MF (Table 2) and later in patients with CML and PV (not shown). Control of thrombocytosis continued to be effective in both groups during a median follow up of 310 days on a maintenance dose of alpha interferon, usually 3 MU t.i.w. (Fig. 1). In patients with ET, alpha interferon had a negligible effect on the haemoglobin level; the white blood cell count dropped during induction treatment but rose to approximately 80% of normal during maintenance (Fig. 2).

Table 1. Frequency and mean time to response in patients with essential thrombocythaemia (ET) and other myeloproliferative disorders (MPD)

		Platelet count	
		< 600 x 10⁹/L	< 400 x 10⁹/L
ET	No. of patients	9/9	6/9
	Mean time (range)	33.4 (8-120) days	95 (30-330) days
Other MPD	No. of patients	8/9	8/9
	Mean time (range)	21.6 (8-60) days	112.5 (30-180) days

Table 2. Mean (± SD) platelet count before and at day 30 of alpha interferon treatment in patients with various myeloproliferative disorders

	Platelet count (x 10⁹/L)		
	Before	Day 30	Reduction %
ET	1.088 ± 369	452 ± 133	58.4
PV	777 ± 69	651 ± 178	16.2
MF	1.677 ± 1.073	608 ± 323	63.7
CML	1.033 ± 165	605 ± 73	39.6

ET = essential thrombocytosis; PV = polycythaemia vera; MF = myelofibrosis; CML = chronic myelogenous leukaemia.

Thrombocytosis-associated symptoms improved or resolved concomitantly with the reduction in platelet count to below 600 x 10⁹/L. Spleen size was reduced in one patient with CML. Marrow reticulin content was moderately to markedly increased at initiation of alpha interferon administration in all patients. Seven patients had repeat bone marrow biopsies before and after teatment. Two of these seven patients (one with ET and one with MF) had a reduction of reticulin from 2+ to 1+ at 5 to 12 months following treatment.

All patients had flu-like symptoms (including fever higher than 38°C) which lasted for up to 4-8 days and were alleviated by paracetamol. Five patients had severe anorexia and weight loss of more than 5 kg. Two patients had severe weakness, and Coombs positive haemolytic anaemia developed in one patient with MF. Alpha interferon treatment has been discontinued in four patients: one at day 90 because of lack of response and cardiac arrhythmia, one at day 120 because of fever (attributed to active tuberculosis), one at day 300 because of recurrence while on treatment and one (a patient with relapsed CML following bone marrow transplantation) on day 210 because of intolerable side effects. The white cell count dropped below 4.0 x 10⁹/L in three patients, and haemoglobin fell below 10g/dL in four. Both were corrected with dose adjustments.

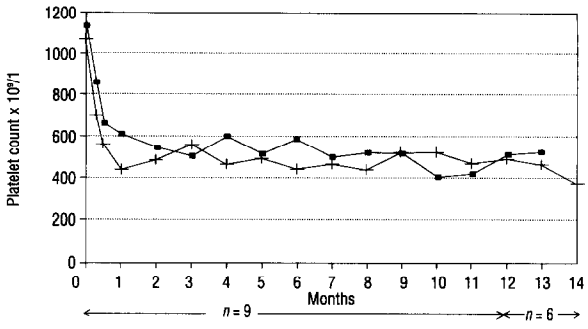

Fig. 1. Fluctuation in mean platelet count in patients with essential thrombocythaemia (+——+) and other myeloproliferative disorders (▪——▪) treated with alpha interferon.

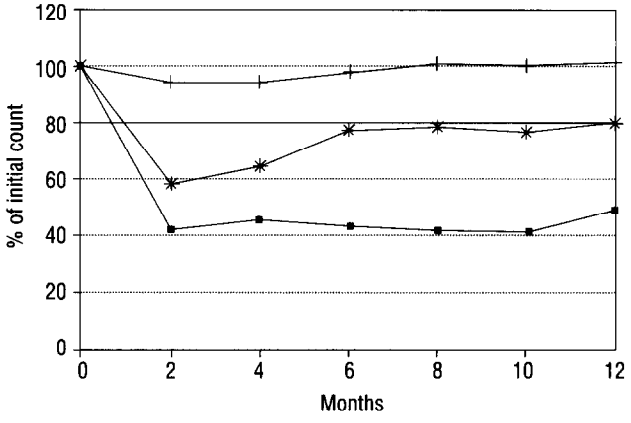

Fig. 2. The effect of alpha interferon on mean platelet count (▪——▪), white blood cells (*——*) and haemoglobin (+——+) in patients with essential thrombocythaemia. (*n* = 9 throughout the 12 months.)

DISCUSSION

Thrombocytosis in MPD has been treated in the past with alkylating agents and ionizing radiation, but these treatments were found to be associated with an increased risk of disease evolution to acute leukaemia [3]. In recent years hydroxyurea has been used in controlled studies [9], but suppression of platelet counts is frequently accompanied or preceded by

granulocytopenia and/or anaemia and the drug's potential mutagenic effect has not been fully evaluated.

Recombinant alpha interferon has been reported to correct excessive thrombocytosis in patients with ET [10] and other MPD [11]. The rationale for the use of alpha interferon in these disorders is based mainly on its general anti-proliferative action [12], which is directed against megakaryocyte progenitor cells [5].

The usual indications for a platelet-lowering treatment are thrombocytosis-associated symptoms or platelet counts above 1000 x 10^9/L. An increased reticulin deposition is frequently found at diagnosis or develops during the evolution of MPD [3]. Only two patients with ET had significant thrombocytosis-associated symptoms, but excessive reticulin deposition was detected in the majority of the patients in the present study. An intramedullary leakage of PDGF from an expanded megakaryocyte pool has been implicated in the pathogenesis of MF [13]. Since the presence of MF was found to have adverse prognostic implications in patients with PV [3], the use of alpha interferon, which inhibits the growth of fibroblast colony-forming units *in vitro* [14], may be directed towards the prevention or reversal of MF.

Our observations indicate that alpha interferon in well-tolerated doses effectively lowers the platelet count in patients with ET and other MPD associated with excessive thrombocytosis. Responses are rapid and are easily maintained for long periods in most patients. In the long term a selective effect on megakaryocytes over white blood cells and red cells may be obtained by adjusting the dose after an initial induction period.

Long-term alpha interferon treatment has been shown to induce cytogenetic remissions in some patients with newly-diagnosed CML [15], although the prognostic significance of this effect has not been established. Similarly, the thrombocytosis-reducing effect of alpha interferon in other clonal MPD looks promising and warrants further investigation.

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