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Alpha Interferon in the Management of Essential Thrombocythaemia

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Thirteen patients (mean age 60.7 years; female:male ratio 10:3) with essential thrombocythaemia were treated with 3 million units (MU)/day interferon alfa-2b subcutaneously (s.c.) for 12 weeks, with all patients requiring a dose reduction after 4 weeks. The mean pretreatment platelet count was 1,400 x 10⁹/L and megakaryocytes were increased in all cases. Splenomegaly was present in six patients and haemorrhagic phenomena were observed in two. Nine patients (69.2%) had objective responses, including two (15.4%) complete responses (platelets < 450 x 10⁹/L) which were then maintained with 5 MU interferon twice a week. Acute toxicity consisted of flu-like symptoms in 12 patients. Chronic toxicity (mainly leucopenia) was observed in nine patients. In conclusion, alpha interferon is a useful agent for the treatment of essential thrombocythaemia, reducing platelet count after initial therapy and then requiring maintenance therapy at a reduced dose. However, the frequent side effects observed make it advisable to use a low dose of interferon alfa-2b, and to treat only those patients with significant symptoms and signs of thrombocytosis.
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INTRODUCTION

ESSENTIAL THROMBOCYTHAEMIA (ET) is a chronic myeloproliferative syndrome characterized by a marked elevation of the platelet count and an excessive proliferation of megakaryocytes in the bone marrow. The increased platelet count in the peripheral blood and the excessive megakaryocyte number reflects the increase in marrow megakaryocyte colony-forming units. The proliferation is clonal [1], and the disorder considered to be rare.

As in other chronic myeloproliferative syndromes, the platelet elevation predisposes the patient to thrombosis and/or haemorrhages. However, as many patients are asymptomatic there is a reluctance to treat ET patients, mainly due to the leukaemogenic effect of many effective agents.

Previous studies have demonstrated the efficacy of alpha interferon in the reduction of the increased platelet levels and organomegaly; interferon alfa-2a [2], interferon alfa-2b [3] and interferon alfa-2c [4] have been employed successfully in ET.

In this report, the efficacy of interferon alfa-2b in the therapy of ET is further evaluated.

PATIENTS AND METHODS

Thirteen cases of ET fulfilling the criteria of the Polycythemia Vera Study Group [5] were treated with interferon alfa-2b. The mean age of the patients was 60.7 years and the female:male ratio 10:3. Seven cases had been treated previously (four received chemotherapy, two anti-platelet agents, and one platelet pheresis). The mean time between diagnosis and alpha interferon therapy was 19.2 months (range 1-56 months). The most relevant clinical findings were splenomegaly, present in six cases, and haemorrhagic phenomena in two. Thrombotic manifestations were not reported (Table 1). Platelet counts ranged between 950 and 2,480 x 10⁹/L (mean 1,400 x 10⁹/L). Bone marrow cellularity was normal in seven cases, increased in five, and decreased in

Table 1. General data

Case no.	Age	Sex	Previous therapy	Clinical data			
				Haemorrhages	Thrombosis	Hepatomegaly	Splenomegaly
1	66	M	APT	-	-	-	+
2	33	M	-	-	-	-	-
3	71	F	6TG	-	-	-	+
4	43	F	Bus	+	-	-	+
5	79	M	-	-	-	+	-
6	68	F	-	-	-	-	-
7	74	F	-	-	-	-	+
8	67	F	-	-	-	-	-
9	54	F	Bus	-	-	-	-
10	65	F	Mel	-	-	-	-
11	40	F	-	-	-	-	+
12	62	F	APT	+	-	-	-
13	67	F	Cytopheresis	-	-	+	+

APT = anti-platelet therapy; 6TG = 6-thioguanine; Bus = Busulphan; Mel = Melphalan; + = present; - = absent.

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Table 2. Biological data

Case	Haemoglobin (g/L)	PCV (L/L)	Leucocytes (x 10⁹/L)	Platelets (x 10⁹/L)	Bone marrow			
					Cellularity	Megakaryocytes	Fibrosis	Karyotype
1	140	0.42	29.0	1,000	+++	++++	A	N
2	160	0.47	9.6	1,500	+	++++	A	N
3	120	0.38	15.9	1,200	+++	++++	A	N
4	136	0.41	8.6	950	+++	++++	A	N
5	139	0.41	12.5	1,200	+++	++++	P(I)	N
6	126	0.39	12.0	1,400	+++/++++	++++	A	N
7	130	0.40	17.0	1,700	+++/++++	++++	A	N
8	126	0.36	7.1	1,300	+++	++++	A	N
9	123	0.36	9.6	1,800	+++/++++	++++	A	N
10	137	0.41	5.6	1,100	+++	++++	P(II)	N
11	150	0.48	14.0	1,040	+++/++++	++++	A	N
12	119	0.42	11.2	1,700	+++	++++	A	N
13	105	0.31	13.0	2,480	+++/++++	++++	P(I)	N

+ = Decreased; ++ = Normal; +++ = Increased; ++++ = Very increased; A = Absent; P = Present; N = Normal.

one; in all cases the megakaryocytes were increased. Bone marrow biopsy showed minimal reticulin fibrosis in two instances and grade II fibrosis in a single case; in the other patients fibrosis was not observed [6] (Table 2).

The dose of alpha interferon employed was 3 million units (MU)/day, subcutaneously, during 12 weeks, administered at 7 p.m. All patients required a reduction in dosage after 4 weeks, in four patients a second reduction was necessary, and in five the therapy was discontinued due to toxicity.

A complete response (CR) was defined as reduction of the platelet count to less than 450 x 10⁹/L maintained for at least 2 months, without palpable spleen or clinical symptoms. Partial response (PR) was defined as the absence of symptoms, with a greater than 50% reduction in spleen size and decrease in platelet count less than the levels for CR.

RESULTS

The duration of therapy was 12 weeks or more in eight cases, 10 weeks in two, 9 weeks in two, and less than 9 weeks in one patient (Table 3). Objective responses (CR + PR) were observed in nine cases (69.2%), two of them being CR (15.4%). The two patients with CRs maintained response for 24 and 41 weeks, respectively; maintenance therapy for these patients was 5 MU of interferon twice a week. Three out of seven cases with PR received 3 and 5 MU of interferon (one and two cases, respectively) (Table 4). All five patients are asymptomatic.

Table 3. Response and toxicity

Case	Response	Induction therapy (weeks)	Toxicity	
			Acute	Chronic
1	F	12	Flu-like syndrome	No
2	F	12	Flu-like syndrome	Leucopenia
3	F	12	Flu-like syndrome	Leucopenia
4	F	10	Flu-like syndrome	Leucopenia
5	CR	12[a]	Flu-like syndrome	No
6	PR	10	Flu-like syndrome	Leucopenia
7	PR	9	Flu-like syndrome	Neurological
8	PR	9	Flu-like syndrome	Metabolic[b]
9	PR	12[a]	No	No
10	CR	12[a]	Flu-like syndrome	Leucopenia/hepatic
11	PR	24[a]	Flu-like syndrome	No
12	PR	8	Flu-like syndrome (+++)	Leucopenia
13	PR	12[a]	Flu-like syndrome	Leucopenia

F = Failure; CR = Complete response; PR = Partial response. +++ = Very increased
[a]Patients on maintenance therapy.
[b]Electrolyte abnormality secondary to diarrhoea.

Table 4. Maintenance therapy

Case	Response	Maintenance therapy (MU twice a week)	Platelet count (x 10⁹/L)
5	CR	5	365
9	PR	5	633
10	PR	3	202
11	PR	5	800
13	PR	5	600

CR = Complete response; PR = Partial response.

Twelve patients developed a flu-like syndrome as an acute toxicity, and in nine chronic toxicity was detected, mainly leucopenia (seven cases). Three patients had neurological, metabolic and hepatic toxicity, respectively, in one case associated with leucopenia (Table 3). The metabolic toxicity consisted of an electrolyte abnormality secondary to diarrhoea.

DISCUSSION

Conventional chemotherapy in ET is directed primarily to the correction of clinical symptoms, organomegaly and platelet count by suppression of megakaryocyte activity with hydroxyurea, busulphan, chlorambucil or 32P. Nevertheless, the potential leukaemogenic effect of these agents has resulted in the need for a non-leukaemogenic myelosuppressive regimen.

In vitro studies have indicated an inhibitory effect of natural interferon on the growth of murine megakaryocyte progenitor cells [7], and a marked suppression of human

megakaryocytopoiesis by alpha interferon [8]. Alpha interferon induced a decrease in the megakaryocyte density and size, suggesting a selective influence on megakaryocytes at various stages of maturation [9]. This is in accordance with a phase I study involving daily administrations of interferon in which a significant reduction in platelet count was observed in several patients within 2 weeks [10].

The effects of alpha, beta and gamma interferon alone or in combination were studied in ET using the mixed colony formation assay. Bone marrow precursors were cultured in the presence of each type of interferon, and the results indicated that alpha interferon would be the best candidate for reducing the megakaryocyte precursors [11].

Alpha interferon has been shown in a number of studies to be a useful agent for ET [3, 4, 12-14]. In the present study the efficacy of alpha interferon (nine responses out of 13 patients) has been confirmed with rapid reductions in platelet levels.

Following the initial reduction in platelet count, maintenance therapy with interferon is required in most patients. In patients who complete the initial course of therapy, excellent therapeutic effects can be achieved on long-term treatment. In our patients, the main problems have been poor tolerance of the induction regimen and leucopenia. Sometimes it is difficult to treat an asymptomatic patient with a drug that has definite clinical side effects, even if they are mild. Moreover, a recent Spanish study [15] has shown a survival curve for ET patients similar to that of a normal age-matched population. This supports the view that therapy for asymptomatic ET should not be based only on a high platelet count.

In conclusion, interferon alfa-2b is a useful agent in the treatment of ET. Nevertheless, the frequent side effects observed in our study and the usual good prognosis make it advisable to reduce the dose of interferon alfa-2b, and to treat only those patients with significant signs and symptoms associated with very high platelet counts.

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Alpha Interferon in Chronic Lymphocytic Leukaemia

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The role of alpha interferon in patients with chronic lymphocytic leukaemia (CLL) has yet to be well established. In studies carried out to date, a significantly higher response rate has been observed in previously untreated patients compared to those who have received prior chemotherapy. Patients with early-stage CLL also respond better than patients with advanced disease. Responses to alpha interferon are transient and complete responses are rare. It is not yet known whether alpha interferon can induce clonal remission, and response is usually measured in terms of the reduction in peripheral blood lymphocyte levels. In one study, a normalization of immunoglobulin levels was observed, and in another there was an increase in the absolute