Giralt (Spain): In my opinion, interferon has a definitive place in ET as in other chronic myeloproliferative diseases; nevertheless, the situation is very different for ET, which is a very chronic and benign disease compared to the other myeloproliferative syndromes, which have lower expected survival times. For old patients, it may be better to begin with chemotherapy and then give interferon, because side effects are not uncommon. We must treat with interferon young patients with symptoms and very important thrombocytosis — perhaps more than a million platelets. I am sure that interferon employed in rather a low dose and probably with a different schedule than I have shown previously will be very useful in ET.

Seewann (Austria): In our experience, the average dosage of interferon necessary to keep platelets below 450 x 10⁹/L is 3-5 MU three times weekly. There are very few patients who need only twice weekly interferon at 3 or 5 MU, and most of the patients get side effects after 9-15 months on this treatment regimen, especially patients in the older age group. With regard to early debulking with an agent such as hydroxyurea, I don't think that this influences the maintenance treatment, because patients respond very quickly to interferon, achieving complete remission in 2 or 3 months. So interferon also induces debulking of disease, but I think the crucial point is the long-term treatment.

Yataganas (Greece): We have had young patients with platelet counts of around 6-700,000 platelets with symptoms. On the other hand, we were amazed to see how extensive a reticulin content there can be at diagnosis in some patients whose platelet count is not as high as one million. So I would say that the indication for treatment should be based on several facts: what agents are available, which are less toxic, presence of symptoms and myelofibrosis, and age.

Question from the floor: I think one should distinguish between other myeloproliferative disorders and ET, which is most often a disease of the young and of long duration. Patients with ET should be treated only if there are symptoms or a very high platelet count. In view of the long duration of the disease and the benign course, one should begin with some non-leukaemogenic therapy, such as (supposedly) hydroxyurea, and give interferon only if there are side effects or resistance to hydroxyurea. The situation is different with chronic myelogenous leukaemia (CML),and here I would use interferon in the case of high platelet counts. For polycythaemia vera, I would use interferon even with platelet counts that are not so high because there are at least two factors of vascular risk. I would like to ask Professor Seewann to comment on the cerebrovascular events in his study - were they young people or old and what was the basic diagnosis?

Seewann (Austria): The patients who had cerebrovascular events were in an age group between 60 and 75 years; one patient had PV and two patients had ET. The patient with PV was, at the time of the cerebrovascular event, in a normal haematocrit range. The platelet count was clearly elevated in two patients and was normal in one ET patient, who had a cerebrovascular event in the first phase of treatment in the 6th week after onset of treatment.

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Alpha Interferon Therapy in the Treatment of Idiopathic Thrombocytopenic Purpura

Stephen J. Proctor

Treatment of patients with idiopathic thrombocytopenic purpura (ITP) varies according to the severity of the condition, the patient's age and the phase of the disease. The mainstay of treatment is corticosteroid therapy, with splenectomy for non-responding patients. For the 5%-10% of patients with refractory disease and bleeding problems, intravenous immunoglobulins are often used. Danazol achieves a response in about 30%-40% of refractory patients. At our centre, we have now treated 13 patients with interferon alfa-2b, all of whom had severe steroid-unresponsive ITP of various durations. All patients received 12 injections of 3 million units (MU) interferon subcutaneously three times a week. The platelet count rose significantly in 10 patients after interferon therapy and in one patient during therapy. Three patients had a complete response and eight a partial response. One complete responder relapsed at 5 months but again responded to retreatment with interferon. Responses were similar in splenectomized and non-splenectomized patients, and platelet-associated immunoglobulin levels remained essentially unchanged. Based on a compilation of data from this and other studies, the positive response rate (platelets at least 30-200 x 10⁹/L for at least 6 weeks) is 69% (22/32 patients). The future role and dosage of interferon in ITP remains to be determined and particularly in direct comparison with intravenous IgG therapy.

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INTRODUCTION

THE CLINICAL manifestations of idiopathic thrombocytopenic purpura (ITP) are related to the haemostatic defect caused by a low platelet count. Haemorrhages, which vary in intensity, are often cutaneous [1]. The incidence of ITP ranges from 6 to 11 cases per 100,000 persons. Women between the ages of 20 and 40 years are affected more commonly than men by a ratio of 3:1 [2]. An increasing incidence of ITP has been observed recently in patients who are positive for human immunodeficiency virus (HIV), including

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male homosexuals, haemophiliacs, and intravenous drug abusers [3]. ITP affects both children and adults.

PATHOPHYSIOLOGY

Accelerated platelet destruction occurring in the reticuloendothelial system (RES) is the key pathophysiological event in ITP. This accelerated destruction is believed to be brought about by the coating of platelets with strongly binding autoantibody [3]. Hence, this condition is also referred to as autoimmune thrombocytopenic purpura.

DISEASE COURSE AND PROGNOSIS

ITP is a heterogeneous condition with a varied clinical course and outcome. It is, however, a relatively benign disorder, with a mortality of approximately 1%-5%, primarily from intracranial bleeding [3].

In children, about 90% of ITP is acute and follows a viral or upper respiratory tract infection. Acute ITP may be caused by immune complexes containing antibodies to viral antigens that cross-react with the platelet surface antigens [2]. Bleeding is usually relatively mild. Fortunately, in approximately 80% of these cases, the thrombocytopenia resolves spontaneously within 6 to 12 months without therapy. In the remaining 10%, the thrombocytopenia persists. Life-threatening intracranial haemorrhage is a particular risk in children, especially when the platelet count is below 20 x 10^9/L [4].

Adults, on the other hand, often have no infectious prodrome and have a more indolent form of ITP that does not show a tendency for spontaneous, long-term remission and that may persist for years or a lifetime. Although spontaneous short-term remissions and relapses may occur, the condition rarely remits permanently without treatment [4].

TREATMENT

Because of the heterogeneity of ITP, treatment approaches vary, depending on the severity of the condition, the patient's age, and the phase of the disease. For instance, in older patients, therapy may not be warranted if the platelet count remains stable above 30 x 10^9/L [4]. In other cases, specific therapy may not be necessary unless the platelet count is less than 20 x 10^9/L or if bleeding is extensive [2]. The main goal of initial therapy, however, should be to obtain a complete remission and to prevent evolution to chronicity [1] with its attendant long-term risk of serious haemorrhage.

The mainstay of treatment in ITP continues to be corticosteroids. In about 50% of patients platelet counts rise within 1-2 weeks, and when normal levels have been achieved the corticosteroid dose can be tapered over a 3-4 week period. If platelet counts fall at this time, they are often maintained on a low dose of steroid.

In situations where a corticosteroid cannot maintain platelet counts at safe levels the next approach, particularly in adult patients, would be to consider splenectomy. Splenectomy is variably effective, but once splenectomy has been performed low-dose corticosteroids can often help to maintain the platelet count at a safe level.

Intravenous immunoglobulin (i.v. IgG) is often used for the 5-10% of patients who have refractory disease with continuing bleeding problems. The problem with the use of i.v. IgG is that it tends to be an expensive product and, though many patients show a response to the treatment, the effect is transient and it is really not possible to maintain patients on such treatment indefinitely.

Immunosuppressive (cytotoxic) agents, including vincristine, vinblastine, cyclophosphamide, and azathioprine, are usually reserved for ITP patients refractory to corticosteroids and splenectomy. Cyclophosphamide and azathioprine may produce a positive response in 1-2 months [5]. In Newcastle upon Tyne, we have used chlorambucil successfully in preference to other alkylating agents and azathioprine. Because immunosuppressants are usually more toxic than other forms of therapy, they should be administered only when other alternatives have been exhausted. Furthermore, since most ITP patients do not have severe bleeding if their platelet counts are greater than 30 x 10^9/L, it is probably safer to avoid more toxic forms of therapy when the counts are above this level.

The synthetic androgen danazol has also been used in severe refractory ITP. Like the glucocorticoids, danazol may modulate the expression of Fc receptors of macrophages and can lead to a modification of lymphocyte subsets. In about 30-40% of patients, a positive response may be seen in about 15-21 days [5].

ALPHA INTERFERON THERAPY

Alpha interferons have only recently been used to treat refractory ITP. The first three cases of chronic, refractory ITP responding to treatment with alpha interferon were reported in 1988 [6]. Preliminary reports showing the value of alpha interferon in virus-associated ITP were also reported by Ellis *et al.* [7] and Lever *et al.* [8].

Ellis *et al.* [7] reported on a 30-year-old male with ITP. He was positive for HIV antibodies and had been a low-grade hepatitis B carrier. His platelet count was 5 x 10^9/L and his bone marrow contained increased numbers of megakaryocytes. His platelet count rose to 66 x 10^9/L while he was taking 60 mg prednisolone daily for 6 weeks. After steroids were discontinued, his platelet count fell but rose to 250 x 10^9/L after daily administration of 0.4 g/kg i.v. IgG for 5 days. Repeat i.v. IgG therapy was given when his platelet count fell below 35 x 10^9/L. Alpha interferon at a dose of 3 million units (MU) was administered subcutaneously (s.c.) on alternate days. Hepatitis B core antigen IgM fell to equivocal values, hepatitis B e antigen became negative, and e antibody appeared. His weekly platelet count rose from 62 x 10^9/L to 110 x 10^9/L. The number of weeks that the platelet count was less than 35 x 10^9/L fell from 10 to 0, and the patient's need for i.v. IgG declined from 15 days to 4 days. After 3 months, alpha interferon was restarted when the platelet count was 28 x 10^9/L. The increase in platelet count was not as steep as during the initial administration of alpha interferon, but the count did not fall below 35 x 10^9/L. The patient did not need further i.v. IgG therapy. When the second course of alpha interferon was started, concentrations of PAIgG and PAIgM were raised, but fell when the platelet count rose. Immune complexes were not detected on the platelets or in serum.

In this patient, treatment with alpha interferon was associated with improvement in platelet counts; it also obviated the need for steroids, reduced the necessity for i.v. IgG, and prevented the need for splenectomy. The investigators noted that the use of steroids or splenectomy in HIV-positive patients can

precipitate Kaposi's sarcoma, opportunistic infections, and metabolic effects.

Lever *et al.* [8] reported on two patients treated with alpha interferon. Their first patient was a 10-year-old boy whose platelet count was less than 30 x 10^9/L and whose bone marrow showed increased megakaryocytes. He was positive for hepatitis B surface and e antigens when ITP was diagnosed. Because he was suspected to have neonatally acquired chronic hepatitis B infection, he was treated with prednisolone 2 mg/kg for 4 weeks. During treatment, platelets rose to normal levels, but returned to pretreatment levels after discontinuation of steroid therapy. A 12-week course of alpha interferon was started at 2.5 MU/m^2 three times a week (t.i.w.). During alpha interferon therapy, the platelet count rose. When treatment was stopped, the platelet count fell and clinical symptoms reappeared. Since the patient did not respond to 40 mg/day prednisolone, splenectomy was performed and his platelet count returned to normal.

The other patient, who was positive for hepatitis B surface antigen and HIV antibody, had a platelet count of 32 x 10^9/L at the age of 35. A year later, in 1985, his platelet count was 1 x 10^9/L. Two courses of i.v. IgG resulted in a short-term rise in the platelet count [8]. Since danazol was ineffective, a third course of i.v. IgG was given, followed by alpha interferon 2.5 MU/m^2 t.i.w. The platelet count rose and clinical signs disappeared. The dose of alpha interferon was gradually increased to 10 MU/m^2, which continued to produce an increase in platelet count, with no tendency for bleeding. The patient continued to receive alpha interferon three t.i.w. for a year.

Even though alpha interferon is antiviral and immunostimulatory, it can inhibit antibody formation. The investigators speculated that alpha interferon may have inhibited viral replication or production of anti-platelet antibodies and that it may be useful non-suppressive treatment for ITP.

INTERFERON ALFA-2b THERAPY

We first used interferon alfa-2b to treat an ITP patient with life-threatening bleeding (Fig. 1) [9]. The patient had not responded to steroids, i.v. IgG, or splenectomy. Chlorambucil, which had been given to reduce putative B-cell clones, produced only transient improvement. We considered interferon alfa-2b to be a non-toxic alternative that might modify B-cell activity involved in antibody production. The patient's platelet count did not rise after 11 s.c. injections of 3 MU interferon alfa-2b administered t.i.w. Therapy was discontinued after the 12th injection when the granulocyte count decreased. Seven to 14 days after therapy was stopped, the platelet count rose exponentially. This rise was sustained with no further therapy for 5 months. At this time, the patient developed severe generalized bleeding and was given three injections of methylprednisolone 250 mg over 24 hours. Since platelet counts did not rise, nine s.c. injections of 3 MU interferon alfa-2b were administered over a 4-week period. Three days after the second course of interferon alfa-2b had been stopped, the platelet count started rising and within 21 days had reached 630 x 10^9/L. We wonder if interferon alfa-2b and methylprednisolone were synergistic in this steroid-non-responsive patient. This second remission has been sustained for more than 1 year without further therapy.

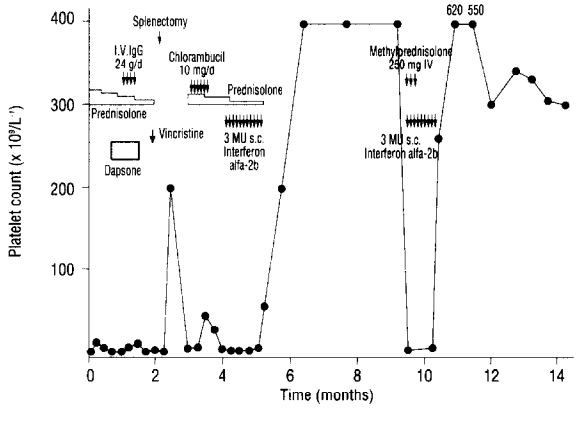

Fig. 1. Therapy and response in patient 1. Intravenous IgG was ineffective in this steroid-insensitive patient. Interferon alfa-2b was administered after partial response to chlorambucil. A second course of interferon alfa-2b was effective 5 months lates. From Proctor *et al.* [9], with permission.

Two subsequent patients who had refused splenectomy were similarly treated with interferon alfa-2b and showed an identical response. We have now treated 13 patients with interferon alfa-2b to assess who would benefit from therapy, its toxicity, and the duration and extent of responses. All patients had severe steroid-non-responsive ITP of various durations (Table 1) [9]. Eight of the 13 patients had elevated levels of PAIgG before interferon alfa-2b treatment. After therapy, PAIgG was measured in eight patients; no significant changes were noted.

Table 1. Previous therapy for ITP in 13 patients

Patient *n*	Sex/age (yr)	Pretreatment PAIgG ratio to normal	Post IFN PAIgG levels	Previous treatment	Prior splenectomy
1a	F/37	+ve 3.0	+ve 3.0	Steroids i.v. IgG Dapsone	Yes
1b	F/37	+ve 3.0	+ve 1.8	Vincristine Chlorambucil	Yes
2	F/70	-ve 1.0	-ve 1.0	Steroids Steroids	No
3	F/65	+ve 2.8	+ve 16.7	Vincristine Danazol Chlorambucil	No
4a	F/18	+ve 6.0	+ve 6.0	Steroids	No
4b	F/18	+ve 6.0	NA	Steroids	No
5	M/40	-ve 1.5	-ve 1.5	Steroids	Yes
6	M/56	+ve 6.3	NA	Steroids i.v. IgG Azathioprine	Yes
7	F/59	+ve 2.2	NA	Steroids i.v. IgG	Yes
8	F/61	+ve 2.2	NA	Steroids	Yes
9	F/41	+ve 1.9	NA	Steroids	Yes
10	F/58	-ve 1.0	-ve 1.0	Steroids	No
11	M/57	-ve 1.5	-ve 1.5	Steroids	Yes
12	F/61	-ve 1.5	-ve 1.5	Steroids i.v. IgG	Yes
13	F/27	+ve 2.3	+ve 2.3	Steroids	No

PAIgG = platelet-associated IgG; IFN = interferon; NA = not available; +ve = positive; -ve = negative. From Proctor *et al.* [9], with permission.

An apparent increase in PAIgG was seen after therapy in one patient.

All patients received 12 s.c. injections of 3 MU interferon alfa-2b t.i.w. Patients on steroid maintenance therapy were continued on their usual dose for the duration of the study. No patient had a concurrent or recent viral infection, and none had clinical or serological evidence of HIV or hepatitis B infection.

All patients tolerated therapy well. Basic haematological parameters and results of interferon alfa-2b therapy are shown in Table 2 [9]. The platelet count rose significantly in 10 patients after interferon alfa-2b therapy and in one patient during therapy. Of the 13 patients, three had a complete response and platelet levels returned to normal within 14 days of stopping therapy. Eight patients had a partial response, with a platelet increase from 30 to 100 x 10⁹/L. Four partial responders had a similar response after a second course of interferon alfa-2b; the remaining four partial responders did not require retreatment. Two patients had a minimal response. One of the complete responders relapsed at 5 months. After another course of interferon alfa-2b, platelets promptly rose above normal levels.

Responses were similar in splenectomized and non-splenectomized patients. Furthermore, since the PAIgG levels remained essentially the same before and after treatment, interferon alfa-2b may act independently of antibody production.

The absolute granulocyte count decreased significantly in the complete responders during interferon alfa-2b treatment, but the decline was not as marked or was absent in the partial or non-responders.

Since our report was published, two similar studies have been conducted. Hurtado *et al.* [10] treated four similar patients using the same patient selection criteria and interferon alfa-2b regimen. Cell immunophenotyping performed before treatment in three patients indicated that all of these patients had a decreased number of CD4 (helper T lymphocytes) antigen-bearing cells and a high proportion of cells bearing HNK-1 (cells with natural killer (NK) activity) antigen. Two of the three patients had high values of CD8 (suppressor T lymphocytes) antigen-bearing cells. None of the three patients showed an abnormal number of cells expressing CD25 (IL-2 receptor) antigen. Clinical characteristics, previous therapy, and laboratory data are given in Table 3 [10].

Platelet counts rose in two patients after the second dose of interferon alfa-2b, but the increase lasted only 2-3 weeks. The other two patients had no change in platelet counts. Immediately after stopping therapy, all patients returned to their original treatments.

Because of the short-term improvement in platelet count in two patients as well as the lack of long-term responses or improvement in bleeding manifestations, the investigators stopped using interferon alfa-2b in refractory ITP. The increased number of circulating cells bearing HNK-1 antigen also led these investigators to question whether interferon therapy was effective in ITP, since interferon stimulates NK activity in these cells.

Bellucci *et al.* [11] treated nine patients with chronic refractory ITP according to the same protocol. A positive response of the platelet count was noted in five patients during therapy, but the response was transient, with a mean duration of fewer than 14 days (Table 4) [11]. No response was seen in the other four patients, nor was a delayed positive response after therapy observed. Platelet counts did not decrease nor did clinical status deteriorate either during interferon therapy or in the months after therapy.

To clarify the varying results with interferon alfa-2b therapy, we compiled data from our study with those from Bellucci [11], Hurtado [10], and other researchers in the United Kingdom to systematize the reports (Table 5) [12]. We classified responses on a simplified scale. Type I indicates a complete response with

Table 2. Basic haematological parameters and results of interferon alfa-2b therapy

Pt no.	Platelet count		Steroid treatment during IFN	Time to maximum response (d)	Neutrophils x 10⁹/L		Total no. of IFN doses (3 x 10⁶)	Duration of response (weeks)
	Pre-IFN	Maximum post-IFN			Pre-IFN	Post-IFN		
1a	6	491	Yes (Reducing dose)	24	3.2	0.98	11	26
1b	5	630	No	46	3.2	1.5	9	28
2	20	202	No	35	12.2	3.0	12	36
3	2	527	Yes (20 mg)	31	8.3	2.8	12	55+
4a	15	57	No	21	4.1	2.1	9	4
4b	14	45	No	23	2.8	1.1	12	3
5	5	9	No	NA	6.5	5.0	12	NA
6	23	56	No	63	2.6	2.3	12	36+
7	18	50	No	35	13.2	12.5	12	5+
8	10	19	Yes (20 mg)	NA	2.9	3.2	12	NA
9	7	154	No	37	NA	NA	12	8
10	14	243	No	10	NA	NA	12	4+
11	14	99	No	64	4.6	2.8	12	15+
12	21	57	No	63	3.23	4.6	12	25+
13	16	111	No	38	10.0	4.56	12	14+

Response to interferon (IFN) occurs in patients whether or not they have had previous splenectomy. Note that the fall in absolute granulocyte count occurred to a greater extent in patients demonstrating complete response. From Proctor *et al.* [9], with permission.

Table 3. Clinical characteristics, previous therapy for ITP and laboratory data

Pt no.	Sex/age (yr)	Previous treatment	CD4 (%)	CD8 (%)	CD25 (%)	HNK-1 (%)	Platelet count (x10⁹/L) Pre-IFN	Maximum during IFN	Maximum post-IFN	Total no. of IFN doses (3 MU)	Last follow-up after IFN withdrawal (d)
1	F/67	Prednisone, splenectomy, danazol, 6-mercaptopurine	ND	ND	ND	ND	9	55	17	12	35
2	F/48	Prednisone, splenectomy, 6-mercaptopurine, vincristine	7 (▼)	2 (▼)	0 (N)	19 (▲)	15	17	12	12	14
3*	F/37	Prednisone, splenectomy, 6-mercaptopurine	0 (▼)	34 (▲)	0 (N)	33 (▲)	30	24	32	12	14
4	M/57	Prednisone, splenectomy, 6-mercaptopurine, cyclophosphamide	17 (▼)	59 (▲)	0 (N)	51 (▲)	12	65	3	9	7

IFN = interferon; ND = not done; ▼, N and ▲ = low, normal and high, respectively, compared with 12 healthy controls (normal ranges: CD4, 25% to 40%; CD8, 15% to 27%, CD25, 0 to 1%; HNK-1, 6% to 16%).
*Concomitantly on prednisone and 6-mercaptopurine. From Hurtado *et al.* [10], with permission.

Table 4. Evolution of platelet count in nine patients treated with interferon alfa-2b

Pt no.	Sex/age (yr)	Pre-treatment platelet count (x10⁹/L)	Maximal platelet count (x10⁹/L)	Time to maximal response (d)	Duration of response (d)	Type of response
1	M/59	35	90	7	< 14	T
2	F/60	20	22	–	–	N
3	F/60	10	22	–	–	N
4	F/65	44	129	14	< 14	T
5*	F/25	10	156	10	< 14	T
6	F/60	8	100	21	< 7	T
7	F/60	20	67	14	< 14	T
8*	F/34	20	9	–	–	N
9*	F/70	74	83	10	–	N

*With corticosteroid therapy; T = transient response; N = negative response. From Bellucci *et al.* [11], with permission.

return of platelet counts above 200 x 10⁹/L for more than 3 months. Type IIa is a partial response with platelet counts between 30 and 200 x 10⁹/L for more than 6 weeks. Type IIb represents a partial response with similar platelet levels maintained less than 6 weeks. Type III is no response with static platelet levels. Type IV is a worsening of the platelet count with increased tendency for bleeding.

Published data were available for 27 patients. Type I responses were seen in three patients. The positive response rate in all patients was 67%, which includes Type I (three patients), Type IIa (eight), and Type IIb (seven). In additon to these published data, unpublished results were available for five other patients treated according to the protocol of Proctor *et al.* [9] Among these, there were three Type I responses, one Type IIb response and one Type III response (Table 5, personal communications).

Table 5. Summary of response to interferon alfa-2b therapy in ITP

Study	Response type I	IIa	IIb	III	IV
Bellucci *et al.* [11]	0	0	5	4	0
Hurtado *et al.* [10]	0	0	1	2	1
Proctor *et al.* [9]	3	8	1	2	0
Total (of 27)	3 (11%)	8 (30%)	7 (26%)	8 (30%)	1 (4%)

Further results provided by personal communications (all patients treated with alpha interferon according to the protocol of Proctor *et al.* [9]): Tucker - $n = 2$: one Type I, one Type IIb; Richardson - $n = 1$: Type III; Rowley - $n = 1$: Type I; Evans - $n = 1$, Type 1.
Type I = complete response, return of platelet count >200 x 10⁹/L for >3 months. Type IIa = partial response, platelet counts between 30 and 200 x 10⁹/L for >6 weeks. Type IIb = partial response, platelet counts between 30 and 200 x 10⁹/L for <6 weeks. Type III = no response, platelet levels remain static; Type IV = worsening of platelet count, increased tendency for bleeding. Data from Proctor *et al.* [12], with permission.

One-third of these responses were transitory. When considering these data, one must bear in mind that all patients had failed standard therapies for prolonged periods. Furthermore, the dose and regimen were an empiric starting point and may not be the optimal regimen for all patients. In non-responders, different doses of interferon alfa-2b may be effective; alternatively, some patients may be totally unresponsive. At the present time, we cannot predict who will respond to interferon alfa-2b treatment.

One of our Type IIa partial responders is epileptic. We re-instituted interferon alfa-2b therapy at the same dose and schedule for 6 months. Platelet count rose from 15 x 10^9/L to 50 x 10^9/L, which has been sustained. Wernli *et al.* [13] reported on two patients who had a transitory response after 12 injections of interferon alfa-2b. Therapy was restarted using 1.5 MU administered s.c. twice a week. After several weeks of therapy, platelet counts increased to normal levels, indicating that low-dose continuous therapy may be beneficial in subgroups of partial responders.

Interferon may directly affect B-cell activity. The NK activity reported by Hurtado *et al.* [10] increases in both responders and non-responders. The suggestion that enhancement of NK activity might worsen ITP seems unlikely and it probably had no effect on the lack of response seen in their patients. Antibodies against interferon may be an alternative explanation for the lack of response seen in some patients. Although there are currently no data on this, the failure of white blood cell counts to decline in interferon non-responders suggests that interferon inhibitors may be present.

Rappaport *et al.* [14] recently reported an interesting case of ITP that occurred 2 years before diagnosis of lung cancer. A 63-year-old male, who was a heavy smoker, had a 2-year history of bruising and episodes of severe epistaxis. The only abnormalities noted on physical examination were petechiae and ecchymosis. Chest X-ray was normal. Neither corticosteroids nor splenectomy were effective. Interferon alfa-2b 3 MU was administered twice a week for 4 weeks. One month later, the patient developed dyspnoea, fatigue and pain on the left side of his chest. Chest X-ray indicated a large tumour of the left lung involving the mediastinum. Biopsy confirmed undifferentiated large cell lung cancer. The authors pointed out that only one other case of ITP preceding a diagnosis of lung cancer had been reported and that ITP might be a prodrome of lung cancer rather than a coincidental concomitant disease. They concluded that interferon alfa-2b should be considered as alternative therapy in cancer patients with symptomatic thrombocytopenia due to an ITP-like syndrome who had failed standard treatments.

The subsequent role and dosage schedules of the alpha interferons in ITP remain uncertain. The initial priority must be to assess the therapy in direct comparison with i.v. IgG in a randomized controlled way. Such a study is planned in the near future.

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DISCUSSION AFTER PROCTOR

Question from the floor: Dr Proctor, if interferon has a late effect in idiopathic thrombocytopenic purpura (ITP) - that is, after stopping treatment platelet count rises - is there any rationale for combining intravenous gammaglobulin for an immediate effect and then interferon for the long-term management of refractory ITP?

Proctor (U.K.): That's a good question. What we are trying to do is determine exactly what interferon will or will not do. I think there is little doubt that in the future there will be a role for combining agents that are known to work in various combinations; but given that the patients are relatively few in number, one has to take one question at a time. One option that I have considered, for example, is the use of long-term chlorambucil and interferon for partial responders. But where you are treating a patient and not simply investigating the effect of an agent, then gammaglobulin and interferon may be used together - I don't think that they are likely to counteract each other in any way, and I suspect that they are likely to have an additive effect. One difference between myself and the French ITP study group is that they have been treating very difficult chronic refractory patients. I think that part of the ITP syndrome is very different to what I have been discussing. I suspect that the complete responses to interferon will be seen in the group that has caused major clinical problems early. The very difficult chronic cases - sometimes, as in this one, associated with other immune problems - are likely to be difficult, although I have heard of someone with rheumatoid factor and an SLE-type syndrome who has had a complete response. So it is going to be very variable.

Question from the floor: I think there are two types of ITP - chronic and acute. Which type of ITP do you think is the more sensitive to interferon?

Proctor (U.K.): I think both are going to be sensitive. I think that for chronic relapsing patients, such as the French group are treating, we should try, as the German investigators did, using low-dose continuous interferon, and not just short courses. I would suspect that this might well produce some improvement of platelet counts.

Question from the floor: Did you have a chance to follow the platelet-associated IgG (PAIgG) levels throughout the course and is there any relationship between the PAIgG levels and type of response?

Proctor (U.K.): We do not have a sensitive enough test to assess this, but the French group have not noticed any change in PAIgG, at least in the short term.