Cancer Chemother Pharmacol (2003) 51: 81–86
DOI 10.1007/s00280-002-0533-4

SHORT COMMUNICATION

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Pilot study of pegylated interferon-alpha 2b in patients with essential thrombocythemia

Received: 16 May 2002 / Accepted: 11 September 2002 / Published online: 21 November 2002

Abstract *Purpose*: Interferon-alpha (IFN-alpha) has been shown to control symptoms, reduce platelet counts, and reduce the bone marrow megakaryocyte mass in patients with essential thrombocythemia (ET). A semisynthetic protein-polymer conjugate of IFN-alpha 2b (PEG-IFN2b) increases the serum half-life of IFN-alpha 2b. We conducted a pilot study of Peg-IFN2b in patients with ET. *Patients and methods*: Patients with a history of persistent (greater than 2 months) platelet counts $>600\times 10^9$/l, with hyperplasia of bone marrow megakaryocytes in the absence of an alternate identifiable cause of thrombocytosis were eligible. Patients were required to have either thrombohemorrhagic signs and/or symptoms if previously untreated; persistence of thrombohemorrhagic signs and/or symptoms if receiving anagrelide, IFN-alpha, or hydroxyurea; or intolerance to anagrelide, IFN-alpha, or hydroxyurea. The initial PEG-IFN2b dose was from 1.5 to 4.5 μg/kg per week subcutaneously with subsequent dose adjustments as indicated by response and adverse events. *Results*: Eleven patients (nine female, median age 54 years, range 26–69 years) were treated. PEG-IFN2b rapidly controlled platelet counts and resolved symptoms in all patients. The median duration of PEG-IFN2b therapy on-study was 9 months (range 4–17 months). No patient had signs or symptoms of thrombosis or hemorrhage while on study. After 2 months of therapy, 10 patients (91%) were in complete remission, and 11 (100%) after 4 months. One patient discontinued therapy at 4 months because of persistent grade 3 fatigue and a second at 5 months because of anxiety and depression. *Conclusion*: PEG-IFN2b has significant activity in patients with ET. Long-term follow-up of a larger cohort of patients is needed to define its role in this disease.

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Keywords Essential thrombocythemia · Pegylated interferon · Efficacy

Introduction

Current therapy for patients with essential thrombocythemia (ET) commonly includes hydroxyurea and/or anagrelide [1, 2]. Concern has been raised about the leukemogenic potential of hydroxyurea [2, 3]. Anagrelide is effective in controlling symptoms and reducing platelet counts in most patients. Anagrelide decreases the bone marrow megakaryocyte mass (BMMM) in patients with ET, primarily by reducing megakaryocyte size and ploidy [4, 5]. Both platelet count elevation and symptoms tend to recur within a short time after discontinuation of anagrelide, even following long-term administration [6].

Overall initial response rates to single-agent anagrelide are over 90% in patients with ET [7]. In one recent study of 35 patients, of 33 (94%) responding patients, 27 (82%) remained on anagrelide therapy for a median of 11 years (range 7–15 years) [6]. Of these patients, 20% experienced a total of ten thrombotic episodes, and a similar proportion experienced major hemorrhagic events. All thrombohemorrhagic complications occurred at a platelet count of more than 400×10^9/l. Thus, for patients who are intolerant of, or fail, anagrelide therapy there is a clear need for alternate approaches.

Recombinant interferon alpha (IFN-alpha) is effective in controlling the platelet counts, reducing symptoms, and reducing the BMMM in patients with ET [8, 9, 10]. However, this therapy is associated with significant adverse events, and up to 20% of patients may have to discontinue within 1 to 3 years [9, 10, 11, 12]. A semisynthetic protein-polymer conjugate of IFN-alpha 2b (PEG-IFN2b) has been created by attaching a 12,000-Da monomethoxypolyethylene glycol (PEG_{12000}) polymer to the native IFN-alpha 2b [13]. PEG_{12000} conjugation increases serum half-life and allows prolonged patient exposure to IFN-alpha 2b [13, 14].

Equivalent units of PEG-IFN2b and IFN-alpha 2b have comparable activity in terms of natural-killer and lymphokine-activated killer cell cytolytic activity induction, induction of class I major histocompatibility proteins, and antiviral activity [13, 15]. Pegylated preparations of IFN-alpha have been studied in patients with chronic viral hepatitis and have been reported to be more effective in comparative studies with IFN-alpha [16, 17, 18]. We conducted a pilot study of PEG-IFN2b in patients with ET.

Materials and methods

Patient eligibility

Patients with a history of persistent (greater than 2 months) platelet counts $>600\times10^9$/l, with hyperplasia of bone marrow megakaryocytes in the absence of an alternate identifiable cause of thrombocytosis were eligible [19]. Patients were required to have a clear indication for therapy, i.e. either (1) ongoing thrombohemorrhagic signs and/or symptoms if previously untreated; (2) persistence of thrombohemorrhagic signs and/or symptoms if receiving anagrelide, IFN-alpha, or hydroxyurea; or (3) intolerance of anagrelide, IFN-alpha, or hydroxyurea. Pretreatment evaluation included history taking and physical examination; complete blood count (CBC), differential, and platelet count; serum chemistries, including liver and renal function studies; bone marrow aspiration with biopsy, cytogenetics, immunophenotyping, molecular studies (including bcr-abl analysis); serum immunoelectrophoresis, serum protein assay, immunoglobulin assay by immunofixation, serum ferritin, vitamin B_{12} and folate levels, autoantibody screen including rheumatoid factor, urinalysis, and radiologic assessments as clinically indicated. Patients were followed-up with physical examination, history, adverse event assessment, CBC, platelet count and serum chemistries, weekly, then monthly or bimonthly as clinically indicated. Bone marrow aspirate and biopsy was repeated every 2 to 3 months for the first 6 months, and every 3 to 4 months thereafter. Cytogenetic and molecular analyses were repeated on all patients within 6 months of going on study.

PEG-IFN2b was supplied by Schering-Plough Laboratories in vials containing 150 mg lyophilized powder, along with sterile water for injection (USP). PEG-IFN2b powder for injection was formulated in single-dose label strengths (150-mg vial), designed to provide the label in a 0.5-ml injection volume. At the time of administration, the vial of PEG-IFN2b powder for injection was reconstituted with 0.7 ml sterile water solution for injection USP to yield 0.74 ml of a 300-mg/ml solution of PEG-IFN2b to be used directly from the vial. In order to ensure the consistent delivery of the label dose in 0.5 ml, an overfill of 0.2 ml was provided to compensate for residual volume in the vial and syringe/needle hub following withdrawal and an additional 0.04 ml overfill was added to compensate for the volume displacement by the excipients during reconstitution of the product. Although the reconstituted solution is stable for 24 h when stored refrigerated between 2 and 8ºC, it was recommended to patients on study that the solution be used within 1 h of mixing.

PEG-IFN2b was given by subcutaneous injection once weekly, either self-administered or by study personnel, at a dose of 3 mg/kg. Dose escalation to 4.5 or 6.0 mg/kg per week for inadequate control of platelet counts or symptoms and dose reduction to 1.5 mg/kg per week for grade 3 or 4 adverse events or if the platelet count was normalized with no symptoms were allowed. A starting dose of 4.5 mg/kg was allowed if the platelet count was $>800\times10^9$/l with moderate to severe thrombohemorrhagic signs or symptoms. A starting dose of 1.5 mg/kg was allowed if the platelet count was $<600\times10^9$/l because of prior therapy with no or mild thrombohemorrhagic symptoms. Premedication with acetaminophen (500–1000 mg) 30 min prior to initial PEG-IFN2b administration and further acetaminophen (500–1000 mg orally every 4–6 h) as needed for 'flu-like adverse events were allowed as long as the total daily dose did not exceed 3000 mg. Other cytotoxic, radiation, colony-stimulating factor, investigational, or biologic therapy was prohibited while the patient was on study.

Response and toxicity criteria

A complete response was defined as persistent (>1 month) reduction of platelets counts to $<400\times10^9$/l with no evident thrombohemorrhagic events. A partial response was defined as persistent (>1 month) reduction of platelets counts to $<600\times10^9$/l but $>400\times10^9$/l with no evident thrombohemorrhagic events. Toxicity was graded on a scale of 0 to 5 using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 criteria.

Results

The clinical characteristics and progress of 11 patients treated on study are summarized in Table 1. Their median age was 55 years (range 26–69 years); two (17%) were older than 60 years. Nine patients (83%) were female. The median duration of prior diagnosis of ET was 40 months (range 2–120 months). The median duration of prior therapy for ET was 25 months (range 0–84 months). In terms of prior anagrelide exposure, two patients on the cohort had received no specific therapy for ET. One patient had received aspirin only and one patient, who had had a previous response to conventional IFN, requested to go on study and had received no prior anagrelide therapy. The remaining seven patients had all received prior anagrelide therapy (Table 1). Three patients were intolerant of anagrelide, usually due to persistent nausea and/or hypotension, while a further four patients had persistent ET-attributable symptoms despite an adequate trial of anagrelide. Seven patients had received prior therapy with anagrelide, four with hydroxyurea, and three with IFN-alpha. All patients had a diploid karyotype. Two patients received a starting dose of PEG-IFN2b of 4.5 mg/kg as they had platelet counts $>800\times10^9$/l with moderate thrombohemorrhagic symptoms. Two patients commenced therapy on study at a weekly dose of 1.5 mg/kg as both had platelet counts $<600\times10^9$/l, were intolerant of anagrelide, and had no thrombohemorrhagic symptoms at the time of going on study. Both patients had histories of prior platelet counts $>1000\times10^9$/l associated with thrombotic symptoms – the platelet counts had normalized with resolution of attributable symptoms in both patients on anagrelide therapy, but this was poorly tolerated due to symptomatic hypotension and persistent nausea in one patient each.

The median duration of PEG-IFN2b therapy on study was 9 months (4–17 months). No patient had signs or symptoms of thrombosis or hemorrhage while on study. Nine patients (82%) were in complete remission at 2 months of therapy, and 11 (100%) at 4 months. This study was terminated when PEG-IFN2b

Table 1 Clinical characteristics and progress of 11 patients treated on study

Patient no.	Sex	Age (years)	Performance score	Diagnosis to study entry (months)	Prestudy therapy	Duration (months)	On-study (months)	CBC						Post-study details
								Baseline			2 months			
								Hemoglobin (g/dl)	WBC ($\times 10^9$/l)	Platelets ($\times 10^9$/l)	Hemoglobin (g/dl)	WBC ($\times 10^9$/l)	Platelets ($\times 10^9$/l)	
1	F	51	0	84	IFNα	84	6	14.9	8.6	957	14.0	3.7	359	Ongoing PEG-IFN2b therapy; >12 months asymptomatic
					Anagrelide	1								
					Pheresis									
2	M	59	0	2	Aspirin	2	17	14.7	7.2	581	12.1	2.8	364	Ongoing PEG-IFN2b therapy; >3 months asymptomatic
3	F	56	0	24	IFNα	24	16	13.4	6.1	352	13.7	7.0	301	Ongoing PEG-IFN2b therapy; >12 months recurrence of carcinoma of tongue
					Anagrelide	1								
4	F	52	1	48	Anagrelide	24	4[a]	11.2	6.6	776	10.9	4.5	276	Lost to follow-up
					Hydroxyurea	4								
5	F	69	0	60	Pheresis		13	14.3	18.2	1170	14.6	8.9	297	Colon cancer diagnosed 6 months after leaving study; intermittent PEG-IFN2b therapy >6 months
					Anagrelide	1								
6	F	58	1	2	–	–	6	12.3	6.9	895	11.4	2.6	251	Intermittent PEG-IFN2b therapy; TIA with small lacunar infarction head of the caudate nucleus
7	M	68	0	26	Hydroxyurea	12	10	14.8	17.2	453	14.7	11.3	329	Lost to follow-up
					Anagrelide	11								
8	F	46	1	3	–	–	10	13.1	11.7	902	12.3	3.5	159	PEG-IFN2b stopped; normal CBC for >6 months; asymptomatic
9	F	26	0	33	IFNα	30	10	12.3	4.6	479	11.8	2.6	234	Lost to follow-up
					Anagrelide	30								
					Hydroxyurea	2								
10	F	53	0	41	Anagrelide	24	5[a]	10.9	8.6	188	12.2	3.7	161	Lost to follow-up
					Hydroxyurea	24								
11	F	51	0	120	Hydroxyurea	72	5	11.6	14.1	303	11.0	5.5	264	Lost to follow-up
					IFNα	4								

[a]Stopped study because of adverse effects

became available commercially, as the patients were then able to receive all care and follow-up from local physicians. Eight patients (73%) experienced grade 2 or 3 'flu-like symptoms, including fever, headache, myalgias, and nausea, following the initial PEG-IFN2b injection. These symptoms were well controlled by acetaminophen and resolved completely in seven patients by the fifth injection. Two of these patients continued to take acetaminophen prior to each injection. One patient had persistent 'flu-like symptoms and eventually discontinued therapy at 4 months, primarily due to grade 3 fatigue. Five patients reported intermittent redness at the injection site; this was not associated with pain or pruritus. Three patients developed alopecia (two mild, one moderate) after 6, 8 and 12 months on study. This resolved completely in all three patients without a specific dose reduction in response. One patient developed a grade 3 hepatic transaminitis with no increase in serum bilirubin after 3 months on a weekly 3 mg/kg regimen, but liver enzymes normalized after reduction to a weekly 1.5 mg/kg regimen. A second patient discontinued therapy after 5 months because of anxiety and depression. This patient had a history of anxiety and depression prior to study entry, and, after an interval of 2 months from leaving the study, received further PEG-IFN2b therapy for ET and at the time of this report had done so for over 3 months without recurrence of these symptoms.

Discussion

The risk/benefit ratio of cytoreductive therapy in patients with ET has not yet been defined and may vary markedly between individuals. Current therapy, for those patients who are deemed to require it, involves a therapeutic calculation between the needs to control platelet counts, thrombohemorrhagic phenomena, adverse effects, and leukemogenic risk [20]. The choice of agent(s) is often affected by the severity of signs and/or symptoms and the patient's age. While hydroxyurea, anagrelide, and IFN-alpha are all effective in controlling blood counts and symptoms, they have markedly different adverse effect profiles and the latter two agents are considered to have minimal or no leukemogenic risk. It may, in both cases, be premature to make a definitive statement on this issue.

Wang et al. have recently reported on the effects of IFN-alpha on megakaryocyte development [21]. Using several bone marrow cell purification techniques and quantitative culture methods, this group demonstrated that IFN-alpha directly inhibits megakaryocyte growth induced by thrombopoietin (TPO). Janus kinase (JAK) and its substrates mediate the effects of TPO on cellular proliferation and survival [22]. Wang et al. found that IFN-alpha directly suppresses TPO-induced phosphorylation of the JAK2 substrates c-Mpl (the TPO receptor) and signal transduction and activation of transcription 5 (STAT5) in a TPO-dependent hematopoietic cell line and of c-Mpl and STAT3 in primary murine megakaryocytes [21]. IFN-alpha induces the production of suppressors of cytokine signaling-1 (SOCS-1) in these cells, which has been shown to inhibit TPO-induced cell growth [23, 24].

A large body of data suggests that IFN-alpha is effective in approximately 60% to 70% of patients with ET over a 1 to 5-year period [8, 9, 25, 26]. However, adverse effects result in discontinuation of INF-alpha in approximately 25% of patients with ET by 1 to 2 years, and are of sufficient severity to require dose reductions in another 20% of patients. INF-alpha reduces BMMM, and thus may be capable of reducing the already low risk that patients with ET will develop leukemia. Sustained remissions in patients with ET have been reported following discontinuation of IFN-alpha therapy [27, 28]. IFN-alpha has been used to successfully treat pregnant patients with ET [29, 30, 31, 32, 33, 34, 35, 36]. Thus a less-toxic form of INF-alpha is of potential therapeutic benefit in patients with ET.

Polyethylene glycol (PEG) is a linear, hydrophobic, uncharged, flexible polymer that is available in a variety of molecular weights. PEG modification of proteins represents a significant current endeavor in protein pharmaceuticals. In studies involving over 40 proteins, PEG modification usually lengthens the plasma half-life, reduces antigenicity and immunogenicity, and reduces sensitivity to proteolysis. Neutralizing antibodies are a significant clinical issue in some patients receiving INF-alpha, with current data indicating that these antibodies occur more frequently and are more frequently associated with loss of clinical benefit in patients with hematologic malignancies rather than solid tumors [37, 38, 39, 40]. PEG-IFN2b was developed as a semisynthetic form (protein-polymer conjugate) of IFN-alpha 2b (intron A) by attaching a PEG molecule to the epsilon amino group of some lysine residues in the protein molecule and/or the N-terminal amino acid. A single PEG_{12000} molecule is conjugated to free amino groups on an intron molecule via a urethane linkage. The PEG-IFN2b conjugate is formulated as a lyophilized powder for injection. The prolongation of plasma half-life with subsequent increase in AUC is hoped to result in enhancement of the therapeutic window for PEG-IFN2b as compared to IFN-2b.

In this pilot study, weekly PEG-IFN2b rapidly controlled the platelet counts and alleviated symptoms in all patients. However, the study regimen was associated with significant toxicities, with 2 of 11 patients discontinuing therapy. Anxiety and depression was the cause of stopping therapy in one patient. An incidence of 16% to 26% of anxiety and/or depression as an adverse event has been reported in studies of PEG-IFN2b in patients with chronic hepatitis [41, 42]. This patient had a history of these symptoms prior to PEG-IFN2b therapy and after the study received further PEG-INF2b therapy without adverse effects. Eight patients (73%) had distressing 'flu-like symptoms with the first dose of therapy and all patients had subsequent dose reductions as their

platelet counts fell and symptoms resolved. Thus, both lower initial and maintenance doses may be more appropriate for future studies.

Initial pilot studies with PEG-IFN2b might reasonably be confined to patients who are intolerant of anagrelide or have failed to completely respond to it. However, as anagrelide is so well tolerated and effective in reducing symptoms, the important stimulus for long-term PEG-IFN2b use, would be the clear demonstration of a progressive reduction in the BMMM and eventually, although these studies would take many years, a clear demonstration that the rate of leukemogenesis or transformation to myelofibrosis were significantly reduced in patients with ET receiving this therapy. For most patients, the optimum regimen may well be a combination in which lower doses of anagrelide, which will thus be extremely well tolerated, will rapidly reduce platelets and symptoms, given with concomitant very low doses of PEG-IFN2b, which will also greatly reduce this drug's adverse effects and allow chronic dosing with a regimen with the potential to significantly reduce or eliminate the malignant clone in ET.

The available data clearly suggest that PEG-IFN2b is superior to unmodified IFN in terms of its adverse event profile and efficacy. However, the experience with PEG-IFN2b is relatively preliminary and longer-term follow-up of larger cohorts of patients will be needed to allow definitive comparisons with the unmodified preparation. Thus, whether the suggested studies utilize pegylated or unmodified IFN will depend on the maturation of the current large PEG-IFN studies. Long-term follow-up of a larger cohort of patients is needed to define the role of PEG-IFN2b in patients with ET. Combinations of anagrelide and PEG-IFN2b may be particularly worthy of study, as this might allow disease control using lower doses of both agents with fewer adverse events while perhaps increasing BMMM reduction.

References

1. Silverstein MN, Petitt RM, Solberg LA Jr, Fleming JS, Knight RC Schacter LP (1988) Anagrelide: a new drug for treating thrombocytosis. N Engl J Med 318:1292
2. Tefferi A, Solberg LA, Silverstein MN (2000) A clinical update in polycythemia vera and essential thrombocythemia. Am J Med 109:141
3. Finazzi G, Barbui T (1999) Treatment of essential thrombocythemia with special emphasis on leukemogenic risk. Ann Hematol 78:389
4. Tomer A (2002) Effects of anagrelide on in vivo megakaryocyte proliferation and maturation in essential thrombocythemia. Blood 99:1602
5. Tefferi A, Silverstein MN, Petitt RM, Mesa RA Solberg LA Jr (1997) Anagrelide as a new platelet-lowering agent in essential thrombocythemia: mechanism of action, efficacy, toxicity, current indications. Semin Thromb Hemost 23:379
6. Storen EC, Tefferi A (2001) Long-term use of anagrelide in young patients with essential thrombocythemia. Blood 97:863
7. Oertel MD (1998) Anagrelide, a selective thrombocytopenic agent. Am J Health Syst Pharm 55:1979
8. Giles FJ, Singer CR, Gray AG, Yong KL, Brozovic M, Davies SC, Grant IR, Hoffbrand AV, Machin SJ, Mehta AB, et al (1988) Alpha-interferon therapy for essential thrombocythaemia. Lancet 2:70
9. Giles FJ (1991) Maintenance therapy in the myeloproliferative disorders: the current options. Br J Haematol 79 [Suppl 1]:92
10. Gisslinger H, Ludwig H, Linkesch W, Chott A, Fritz E Radaszkiewicz T (1989) Long-term interferon therapy for thrombocytosis in myeloproliferative diseases. Lancet 1:634
11. Bentley M, Taylor K, Grigg A, Kronenberg H, Gibson J, Bunce I, Eliadis P, Olsen T, Wright S, Taylor D, Rodwell R (1999) Long-term interferon-alpha 2A does not induce sustained hematologic remission in younger patients with essential thrombocythemia. Leuk Lymphoma 36:123
12. Gisslinger H, Chott A, Scheithauer W, Gilly B, Linkesch W Ludwig H (1991) Interferon in essential thrombocythaemia. Br J Haematol 79 [Suppl 1]:42
13. Grace M, Youngster S, Gitlin G, Sydor W, Xie L, Westreich L, Jacobs S, Brassard D, Bausch J Bordens R (2001) Structural and biologic characterization of pegylated recombinant IFN-alpha2b. J Interferon Cytokine Res 21:1103
14. Wang YS, Youngster S, Bausch J, Zhang R, McNemar C, Wyss DF (2000) Identification of the major positional isomer of pegylated interferon alpha-2b. Biochemistry 39:10634
15. Glue P, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, Salfi M, Jacobs S, Clement RP (2000) A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Therapy Group. Hepatology 32:647
16. Perry CM, Jarvis B (2001) Peginterferon-alpha-2a (40 kD): a review of its use in the management of chronic hepatitis C. Drugs 61:2263
17. Kozlowski A, Charles SA Harris JM (2001) Development of pegylated interferons for the treatment of chronic hepatitis C. Biodrugs 15:419
18. Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, Schiff ER, Goodman ZD, Laughlin M, Yao R, Albrecht JK (2001) A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology 34:395
19. Michiels JJ, Juvonen E (1997) Proposal for revised diagnostic criteria of essential thrombocythemia and polycythemia vera by the Thrombocythemia Vera Study Group. Semin Thromb Hemost 23:339
20. Briere J, Guilmin F (2001) Management of patients with essential thrombocythemia: current concepts and perspectives. Pathol Biol (Paris) 49:178
21. Wang Q, Miyakawa Y, Fox N Kaushansky K (2000) Interferon-alpha directly represses megakaryopoiesis by inhibiting thrombopoietin-induced signaling through induction of SOCS-1. Blood 96:2093
22. Drachman JG, Kaushansky K (1997) Dissecting the thrombopoietin receptor: functional elements of the Mpl cytoplasmic domain. Proc Natl Acad Sci U S A 94:2350
23. Hilton DJ (1999) Negative regulators of cytokine signal transduction. Cell Mol Life Sci 55:1568
24. Alexander WS, Starr R, Metcalf D, Nicholson SE, Farley A, Elefanty AG, Brysha M, Kile BT, Richardson R, Baca M, Zhang JG, Willson TA, Viney EM, Sprigg NS, Rakar S, Corbin J, Mifsud S, DiRago L, Cary D, Nicola NA, Hilton DJ (1999) Suppressors of cytokine signaling (SOCS): negative regulators of signal transduction. J Leuk Biol 66:588
25. Sacchi S, Gugliotta L, Papineschi F, Liberati AM, Rupoli S, Delfini C, Ruggeri M, Cavanna L, Bucalossi A, Benedetti E, Ferrandina C, Vinci G, Morselli M, Torelli G (1998) Alfa-interferon in the treatment of essential thrombocythemia: clinical results and evaluation of its biological effects on the hematopoietic neoplastic clone. Italian Cooperative Group on ET. Leukemia 12:289
26. Velu T, Delwiche F (1988) Treatment of essential thrombocythaemia by alpha-interferon. Lancet 2:628
27. Kasparu H, Bernhart M, Krieger O, Lutz D (1992) Remission may continue after termination of rIFN alpha-2b treatment for essential thrombocythemia. Eur J Haematol 48:33

28. Sacchi S, Tabilio A, Leoni P, Riccardi A, Vecchi A, Messora C, Bensi L, Falzetti F, Rupoli S Ucci G, et al (1993) Sustained complete hematological remission in essential thrombocythemia after discontinuation of long-term alpha-IFN treatment. Ann Hematol 66:245
29. Vantroyen B, Vanstraelen D (2002) Management of essential thrombocythemia during pregnancy with aspirin, interferon alpha-2a and no treatment. A comparative analysis of the literature. Acta Haematol 107:158
30. Cincotta R, Higgins JR, Tippett C, Gallery E, North R, McMahon LP, Brennecke SP (2000) Management of essential thrombocythaemia during pregnancy. Aust N Z J Obstet Gynaecol 40:33
31. Iki S, Usuki K, Kotaki M, Yamaguchi Y, Urabe A (1999) Successful pregnancy and delivery during alpha-interferon therapy for essential thrombocythemia (in Japanese). Rinsho Ketsueki 40:1201
32. Delage R, Demers C, Cantin G, Roy J (1996) Treatment of essential thrombocythemia during pregnancy with interferon-alpha. Obstet Gynecol 87:814
33. Milano V, Gabrielli S, Rizzo N, Vianelli N, Gugliotta L, Orsini LF, Baravelli S, Pilu GL, Bovicelli L (1996) Successful treatment of essential thrombocythemia in a pregnancy with recombinant interferon-alpha 2a. J Matern Fetal Med 5:74
34. Williams JM, Schlesinger PE, Gray AG (1994) Successful treatment of essential thrombocythaemia and recurrent abortion with alpha interferon. Br J Haematol 88:647
35. Vianelli N, Gugliotta L, Tura S, Bovicelli L, Rizzo N Gabrielli A (1994) Interferon-alpha 2a treatment in a pregnant woman with essential thrombocythemia. Blood 83:874
36. Thornley S, Manoharan A (1994) Successful treatment of essential thrombocythemia with alpha interferon during pregnancy. Eur J Haematol 52:63
37. Grossberg SE, Kawade Y, Kohase M, Klein JP (2001) The neutralization of interferons by antibody. II. Neutralizing antibody unitage and its relationship to bioassay sensitivity: the tenfold reduction unit. J Interferon Cytokine Res 21:743
38. Oberg K, Alm G (1997) The incidence and clinical significance of antibodies to interferon-a in patients with solid tumors. Biotherapy 10:1
39. Steinmann GG, God B, Rosenkaimer F, Adolf G, Bidlingmaier G, Fruhbeis B, Lamche H, Lindner J, Patzelt E, Schmahling C, et al (1992) Low incidence of antibody formation due to long-term interferon-alpha 2c treatment of cancer patients. Clin Investig 70:136
40. McSweeney EN, Giles FJ, Worman CP, Jewel AP, Tsakona CP, Hoffbrand AV, Mehta AB, Newland AC, Cawley JC, Galvani D, et al (1993) Recombinant interferon alfa 2a in the treatment of patients with early stage B chronic lymphocytic leukaemia. Br J Haematol 85:77
41. Heathcote EJ, Shiffman ML, Cooksley WG, Dusheiko GM, Lee SS, Balart L, Reindollar R, Reddy RK, Wright TL, Lin A, Hoffman J, De Pamphilis J (2000) Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 343:1673
42. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, O'Grady J, Reichen J, Diago M, Lin A, Hoffman J, Brunda MJ (2000) Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 343:1666