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Brief report

Recombinant interferon-α may retard progression of early primary myelofibrosis: a preliminary report

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The limited effects of current treatments of primary myelofibrosis (PM) led us to prospectively evaluate recombinant interferon-α (rIFNα) in "early" PM patients with residual hematopoiesis and only grade 1 or 2 myelofibrosis. Seventeen patients meeting World Health Organization PM diagnostic criteria received either rIFNα-2b 500 000 to 3 million units 3 times weekly, or pegylated rIFNα-2a 45 or 90 μg weekly. International Working Group for Myelofibrosis Research and Treatment criteria for prognosis and response were used. Eleven patients were women and 6 were men. Their median age at diagnosis was 57 years. Eleven patients were low risk and 6 were intermediate-1 risk. Two achieved complete remission, 7 partial, 1 clinical improvement, 4 stable disease, and 3 had progressive disease. Thus, more than 80% derived clinical benefit or stability. Improvement in marrow morphology occurred in 4. Toxicity was acceptable. These results, with documented marrow reversion because of interferon treatment, warrant expanded evaluation. (*Blood*. 2011;117(24):6669-6672)

Introduction

Limitations of conventional treatment, *JAK2* inhibitors, and stem cell transplantation in primary myelofibrosis (PM)[1-4] led us to explore recombinant interferon-α (rIFNα) in "early" PM, when there is residual hematopoiesis and only grade 1 or 2 fibrosis. This use of rIFNα is based on its effectiveness in treating polycythemia vera with fibrosis[5-8] and its biologic effects on megakaryopoiesis and hematopoietic stem cells.[9] It is agreed that rIFNα is not beneficial in advanced PM, when the marrow is extensively fibrotic and/or osteosclerotic without residual hematopoietic cells.[10,11] Thus, the use of rIFNα in early PM[10-13] is not competitive with *Janus kinase* inhibitors and immunomodulatory drugs, which are used in advanced PM.[1-3] We previously described preliminary results of rIFNα-2b therapy in 13 patients with early PM,[14] of whom 4 had documented significant marrow change. We now report updated, detailed results of this prospective, single-center analysis, expanded to include 17 patients, of whom 3 received pegylated rIFNα-2a (peg-IFNα-2a) therapy.

Methods

Diagnosis was established using World Health Organization criteria for PM.[15] Marrow specimens were stained with hematoxylin-eosin, Giemsa, and for reticulin and collagen. Fibrosis was graded using Manoharan criteria.[16] Patients with grade 3 or 4 reticulin were excluded.[16] Included patients had residual erythropoietic foci occupying ≥ 30% of the marrow biopsy (Figure 1A).

Prognosis and response were assessed using International Working Group for Myelofibrosis Research and Treatment criteria.[17-19] Inclusion categories were low-risk and intermediate-1 risk. Response classifications included: complete response (CR), partial response (PR), clinical improvement (CI), stable disease (SD), and progressive disease (PD).

After obtaining informed consent, baseline evaluations were performed, including history, physical examination, complete blood count, differential, serum chemistries, liver, renal, and thyroid function tests, bone marrow biopsy, BCR-ABL determination, cytogenetic evaluation, and *JAK2* analysis. Spleen size was measured in centimeters below the left costal margin. Contraindications to rIFNα included depression, neuropathy, thyroid dysfunction, autoimmune disease, and significant hepatic, renal, or cardiac abnormalities. *JAK2* genotyping was performed according to described methods.[20,21] Sequential $JAK2^{V617F}$ responses were evaluated using European LeukemiaNet criteria.[22] Categories included complete, partial, and no molecular response.

We evaluated 62 patients meeting World Health Organization PM criteria, of whom 44 were excluded because of marked marrow fibrosis. The remaining 18 patients (29%) met study inclusion criteria; 17 elected IFN therapy. Eleven were women and 6 were men. None had received prior PM therapy except aspirin. None were transfusion dependent. Their median age at diagnosis was 57 years (range, 36-71 years).

Fourteen received rIFNα-2b 500 000 to 1 million units subcutaneously 3 times weekly, gradually increasing to 2 million to 3 million units 3 times weekly as tolerated and, if necessary, to reduce spleen size, which was used as a clinical indicator of response. Three patients received 45 or 90 μg of peg-IFNα-2a weekly because of patient preference and insurance coverage. Patients were evaluated at 2- to 3-month intervals. Marrow biopsy was attempted annually. Toxicity was assessed using the Common Terminology Criteria, Version 3.0. We subsequently administered the minimum dose of therapy to achieve the maximum effect. Dose adjustments were made by taking into account resolution of splenomegaly, and toxicity, if present. Study period and therapy duration were equivalent: median, 3.3 years (range, 0.5-15.0 years). One patient in our original report,[14] who had a marrow remission after 1 year, received subsequent care elsewhere. Because appropriate follow-up data could not be obtained, this patient was excluded from the analysis.

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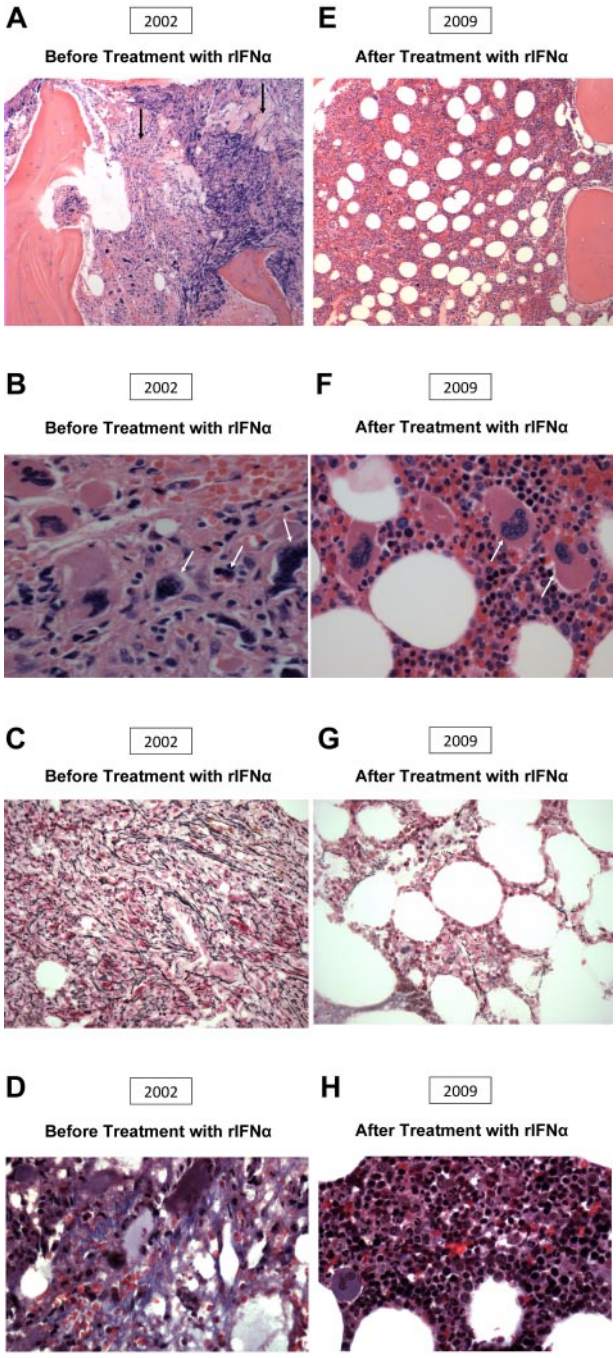

Figure 1. Morphologic change after IFN therapy in a patient with primary myelofibrosis. (A-D) Before treatment (2002). (A) The area of myelofibrosis (left), with preserved residual foci of hematopoiesis, and abnormal megakaryocyte morphology (right). (B) Abnormal megakaryocyte morphology. (C) 2+ reticulin fibrosis. (D) Collagen fibrosis. (E-H) After treatment (2009). (E) Improved bone marrow architecture, hematopoiesis, and megakaryocyte morphology. (F) Improved megakaryocyte morphology and increased normoblastic erythropoiesis. (G) Minimal reticulin fibrosis. (H) Absent collagen fibrosis.

Results and discussion

Eleven patients were low-risk and 6 were intermediate-1 risk (Table 1). Responses were seen in both categories. Two achieved CR, 7 PR, 1 CI, 4 SD, and 3 PD. Ten (58.8%) derived clinical benefit, and another 4 (23.5%) disease stability. Thus, > 80% derived clinical benefit or stability. Seven of 11 low-risk patients (63.6%), and 3 of 6 intermediate-1 risk patients (50.0%) showed clinical benefit. Three of 11 low-risk patients (27.3%) and 1 of 6 intermediate-1 risk patients (16.7%) had disease stability. The median time to any documented response was 1.0 year (range, 0.4-7.4 years); the median duration after any documented response has been 2.0 years (range, 0.1-14.0 years).

Median baseline leukocyte, hematocrit, hemoglobin, and platelet values were 8.7 ×1000/μL, 35.5%, 11.7 g/dL, and 404 000/μL, respectively. Median values at last follow-up were 5.7 ×1000/μL, 34.5%, 11.5 g/dL, and 270 000/μL, respectively, thus remaining relatively unchanged.

Nine of 15 patients with initial splenomegaly had complete resolution of splenomegaly. Fifteen of 17 patients had either sustained reduction in spleen size or no splenomegaly without progression (Table 1).

Marrow follow-up studies, possible in 15, were performed a median of 3.2 years (range, 0.9-7.6 years) after therapy start. Marrow morphology remained unchanged in 11 but significantly improved in 4 (2 CR and 2 PR) after a median of 3.0 years (range, 1.0-7.4 years). The median marrow response duration after documentation has been 1.9 years (range, 0.4-14.0 years). Marrow architecture, reticulin and collagen fibrosis, and megakaryocytic atypia significantly improved in all 4, and fibrosis and megakaryocytic atypia were virtually absent in 2 after 1.0 to 4.0 years (Figure 1E-H). In these 4 patients, sustained reduction in splenomegaly occurred. Three had normal cytogenetics, and 1 had trisomy 1q, which has persisted. Only 2 have had partial molecular response.

Of the 17 patients, sequential cytogenetic analyses were possible in 4 of 5 with abnormal cytogenetics and showed no evolution or resolution of these abnormalities. Sequential analyses, possible in 7 with initially normal karyotypes, did not change. Cytogenetic abnormalities were as previously described in PM.[23,24] One patient with 20q− had PD.[23-25] Except for this patient, contrary to other reports,[23,24] neither favorable nor unfavorable cytogenetics correlated with treatment response or disease progression.

Quantitative $JAK2^{V617F}$ allele burden was assessed in 17 patients. Five of these 17 had wild-type and 12 had mutant forms of the *JAK2* allele (median allele burden, 17 patients: 10.7%; range, 2.0%-88.1%). Of 16 with serial quantitative $JAK2^{V617F}$ analyses (average number of determinations = 3), 2 achieved partial molecular response and 14 no molecular response (Table 1).[22] Importantly, there was no correlation between change in $JAK2^{V617F}$ allele burden and changes in spleen size or abnormal marrow morphology.

Toxicity was generally mild (grade 1 or 2), dose-related, and subsided or diminished on dose reduction. Eleven patients received continuous therapy, and 6 patients received intermittent therapy. Nine experienced systemic toxicity, 11 hematologic toxicity, and 10 metabolic toxicity. Systemic toxicity included the usual grade 1 or 2 adverse events (eg, asthenia, fatigue, myalgia), which did not require dose reduction. Seven experienced anemia (2 grade 1, 4 grade 2, and 1 grade 4). Five experienced thrombocytopenia (2 grade 1, 2 grade 2, and 1 grade 3). Three experienced grade 1 leukopenia. None required transfusion therapy during treatment with IFN. Nine had grade 1 or 2 liver function test abnormalities, which usually resolved spontaneously. Two experienced continuing slight hyperbilirubinemia. Three experienced grade 1 hypocalcemia, 1 of whom received peg-rIFNα-2a. One patient developed hyperthyroidism, requiring rIFNα-2b discontinuation. Of the 3 treated with peg-rIFNα-2a, 2 experienced grade 1 constitutional toxicity, whereas 1 developed grade 4 anemia and discontinued therapy.

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Table 1. Assessment of prognosis and response

Baseline IWG-MRT prognostic risk group	rIFNα duration, y	IWG-MRT response type	Histologic bone marrow response? (yes/no)	Spleen size before therapy, cm	Spleen size at last follow-up, cm	*JAK2*^{V617F} (initial), %	*JAK2*^{V617F} (final), %	Molecular response§
Low*	7.6	CR	Yes	2	0	ND	ND	None
Low	5.2	PR	No BM follow-up	1	0	ND	NA	NA
Low	7.8	PR	No	0	0	9.7	14.3	None
Low	1.8	PR	Yes	12	0	33.2	38.0	None
Low	2.3	PR	No	16	0	75.4	52.0	Partial
Low	0.5†	PR	No	2	0	20.5	18.3	None
Low*	4.7	CI	No	10	0.5	34.9	29.9	None
Low	0.8	SD	No	11	10	85.8	87.1	None
Low*	15.0	SD	No	7	0	ND	ND	None
Low	2.0‡	SD	No	2	0	ND	ND	None
Low	3.2	PD	No	7	11	2.0	18.0	None
Intermediate-1	4.5	CR	Yes	3	0	10.7	5.3	Partial
Intermediate-1	4.5	PR	No	0	0	45.6	24.1	None
Intermediate-1	3.3†	PR	Yes	3	0	10.1	8.0	None
Intermediate-1	2.9	SD	No BM follow-up	24	16	88.1	89.0	None
Intermediate-1*	5.4	PD	No	16	20	ND	ND	None
Intermediate-1*	2.4†	PD	No	32	24	64.2	50.4	None

BM indicates bone marrow; ND, not detected; and NA, not available.
*Abnormal cytogenetics.
†Received pegylated rIFNα-2a therapy.
‡Discontinued interferon.
§According to European LeukemiaNet Criteria.

In this small sample, it was difficult to assess quantitative differences between rIFNα-2b and peg-rIFNα-2a. One patient receiving peg-rIFNα-2a had a marrow response, and 2 had spleen responses. We think that the low molecular response rate in our peg-rIFNα-2a–treated patients may be related to short therapy duration (Table 1).[7-9,12]

This use of low-dose rIFNα in morphologically "early" PM, as defined, resulted in marrow reversion, regression of splenomegaly, and disease stabilization, with tolerable toxicity. Marrow improvement correlated with splenomegaly regression, suggesting that change in splenomegaly may be used to gauge potential marrow response. Although we, like others, have reported the clinical benefits of rIFNα,[10-13] this is the first series of documented marrow responses with rIFNα therapy correlated with clinical improvement using new criteria for evaluation.[19] These encouraging results warrant further systematic evaluation of IFN in early PM, which as yet remains an experimental therapy.

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Authorship

Contribution: R.T.S. designed and performed the research, cared for the patients, analyzed the data, reviewed histopathology, and wrote the paper; and K.V. and J.J.G. collected and analyzed data and assisted with writing of the paper.

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This review of patients treated with IFN was approved by the Weill Cornell Medical College Institutional Review Board.

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References

1. Mesa RA. How I treat symptomatic splenomegaly in patients with myelofibrosis. *Blood.* 2009; 113(22):5394-5400.
2. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med.* 2010;363(12):1117-1127.
3. Vannucchi AM. From pallation to targeted therapy in myelofibrosis. *N Engl J Med.* 2010;363(12): 1180-1182.
4. Kröger N, Mesa RA. Choosing between stem cell therapy and drugs in myelofibrosis. *Leukemia.* 2008;22(3):474-486.
5. Silver RT. Treatment of polycythemia vera. *Semin Thromb Hemost.* 2006;32(4):437-442.
6. Silver RT. Long-term effects of the treatment of polycythemia vera with recombinant interferon-α. *Cancer.* 2006;107(3):451-458.
7. Kiladjian JJ, Cassinat B, Tulure P, et al. High molecular response rate of polycythemia vera patients treated with pegylated interferon alpha-2a. *Blood.* 2006;108(6):2037-2040.
8. Quintás-Cardama A, Kantarjian H, Manshouri T, et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol.* 2009; 27(32):5418-5424.
9. Lu M, Zhang W, Li Y, et al. Interferon-alpha targets JAK2F617F-positive hematopoietic progenitor cells

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and acts through the p38 MAPK pathway. *Exp Hematol.* 2010;38(6):472-480.

10. Hasselbalch HC. Myelofibrosis with myeloid metaplasia. The advanced phase of an untreated disseminated hematological cancer: time to change our therapeutic attitude with early upfront treatment? *Leuk Res.* 2009;33(1):11-18.
11. Bachleitner-Hofmann T, Gisslinger H. The role of interferon-alpha in the treatment of idiopathic myelofibrosis. *Ann Hematol.* 1999;78(12):533-538.
12. Ianotto JC, Kiladjian JJ, Demory JL, et al. PEG-IFN-alpha-2a therapy in patients with myelofibrosis: a study of the French Groupe d'Etudes des Myelofibroses (GEM) and France Intergroupe des syndromes Myéloprolifératifs (FIM). *Br J Haematol.* 2009;146(2):223-225.
13. Jabbour E, Kantarjian H, Cortes J, et al. PEG-IFN-alpha-2b therapy in BCR-ABL-negative myeloproliferative disorders: final result of a phase 2 study. *Cancer.* 2007;110(9):2012-2018.
14. Silver RT, Vandris K. Recombinant interferon alpha (rIFNα-2b) may retard progression of early primary myelofibrosis [letter]. *Leukemia.* 2009; 23(7):1366-1369.
15. Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. *Blood.* 2007;110(4):1092-1097.
16. Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukaemia in adults. *Br J Haematol.* 1979;43(2):185-190.
17. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood.* 2009;113(13):2895-2901.
18. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood.* 2010;115(9):1703-1708.
19. Tefferi A, Barosi G, Mesa RA, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). *Blood.* 2006; 108(5):1497-1503.
20. Chen Q, Lu P, Jones AV, Cross NC, Silver RT, Wang YL. Amplification refractory mutation system, a highly sensitive and simple polymerase chain reaction assay, for the detection of JAK2V617F mutation in chronic myeloproliferative disorders. *J Mol Diagn.* 2007;9(2):272-276.
21. Jones AV, Silver RT, Waghorn K, et al. Minimal molecular response in polycythemia vera patients treated with imatinib or interferon alpha. *Blood.* 2006;107(8):3339-3341.
22. Barosi G, Birgegard G, Finazzi G, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. *Blood.* 2009; 113(20):4829-4833.
23. Hussein K, Pardanani AD, Van Dyke DL, Hanson CA, Tefferi A. International Prognostic Scoring System-independent cytogenetic risk categorization in primary myelofibrosis. *Blood.* 2010;115(3):496-499.
24. Tam CS, Abruzzo LV, Lin KI, et al. The role of cytogenetic abnormalities as a prognostic marker in primary myelofibrosis: applicability at the time of diagnosis and later during disease course. *Blood.* 2009;113(18):4171-4178.
25. Schaub FX, Jäger R, Looser R, et al. Clonal analysis of deletions on chromosome 20q and JAK2-V617F in MPD suggests that del20q acts independently and is not one of the predisposing mutations for JAK2-V617F. *Blood.* 2009;113(9): 2022-2027.

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