Experience with pegylated interferon α-2a in advanced myeloproliferative neoplasms in an international cohort of 118 patients

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ABSTRACT

The Philadelphia negative myeloproliferative neoplasms, including polycythemia vera, essential thrombocythemia, and myelofibrosis, are associated with substantial vascular and transformative complications. Standard therapy for high-risk disease, particularly in patients that have failed initial therapy, remains controversial. Non-pegylated interferon has previously been shown to be effective in controlling erythrocytosis, thrombocytosis and thrombotic complications, but was found to have poor tolerability and excessive adverse effects. Recently, pegylated interferon alpha-2a was introduced and found to be better tolerated and less toxic than standard interferon. In addition, in recent phase II trials, pegylated interferon alpha-2a therapy was found to induce both hematologic and molecular remissions. We retrospectively analyzed 118 myeloproliferative patients who underwent pegylated interferon alpha-2a treatment. Responses were evaluated by ELN, IWG-MET and EUMNET standardized criteria sets and adverse effects were analyzed.

Key words: myeloproliferative neoplasms, pegylated interferon alpha-2a, response.

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Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF) are clonal BCR-ABL negative myeloproliferative neoplasms (MPNs) associated with increased risk of thrombotic and hemorrhagic complications. Current therapy of Philadelphia negative MPNs depends on risk stratification and estimation of the likelihood of thrombotic and hemorrhagic events. Low-risk disease is often managed with low-dose aspirin alone in ET or with combination therapy of aspirin and phlebotomy in PV. In high-risk MPNs, cytoreduction is often necessary to reduce event rates and hydroxyurea has become accepted as the gold standard for first-line therapy. Currently, there is no standard second-line therapy for patients who have failed initial treatment. Interferon (IFN) has been shown to be effective in controlling erythrocytosis, thrombocytosis and thrombotic complications in previous studies, but was also found to be quite toxic and the dosing schedule was cumbersome.[1,2] The pegylated form of IFN alpha 2a (PegIFN2a) has been evaluated in previous phase II trials and has been shown to be effective and better tolerated than standard IFN. In these studies, hematologic responses were noted to be significant and durable.[3-6] In contrast to standard IFN, PegIFN2a has a superior pharmacokinetic profile and a more convenient dosing schedule and therefore IFN-based therapy has reemerged in the treatment armamentarium for this spectrum of disorders. In addition, a recent phase II trial demonstrated a significant reduction in the $JAK2^{V617F}$ alleic burden among patients with PV and ET, with continued suppression in a small group of patients with PV who stopped treatment.[3] Although hydroxyurea (HU) has been shown to possess the ability to reduce allelic burden in some studies, this effect is not maintained off treatment. There is also controversy regarding HU's link to leukemogenic transformation with long-term use.[7] Furthermore, PegIFN2a has no association with leukemic transformation and may, therefore, be a preferential agent in some patients. Here we report our experience with 118 patients with PV, ET and MF treated with PegIFN2a in a non-trial clinical setting.

Design and Methods

This study included 118 MPN patients treated with PegIFN2a at hematology clinics from eight academic centers in the US and European Union. The patients were retrospectively analyzed as a consecutive cohort of MPN patients treated with PegIFN2a therapy outside clinical trials at each participating center after receiving Institutional Review Board approval. There were no exclusion criteria.

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Each site recorded starting, maximum and final treatment dosages, as well as dosage adjustments. Adverse effects were graded according to Common Terminology Criteria for Adverse Events (CTCAE 3.0). European Leukemia Net (ELN) criteria were used to measure response in PV and ET. The International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) and European Myelofibrosis Network (EUMNET) criteria were used to evaluate response in MF.[8-10] Raw data and response assessment was adjudicated by each of the sites, and were reviewed and confirmed by the first and senior authors.

Results and Discussion

The results of these cases and analysis have not been previously reported. In the overall MPN cohort (Table 1), the median age of diagnosis was 49 years and the female to male ratio was 1.5 to 1. A large proportion were Jak-2 mutation positive (76 patients, 64%), with the largest contribution from the PV subgroup (50 patients, 91%). Splenomegaly was present in 28 patients (23%) of the total MPN cohort, with 47% of MF patients presenting this clinical characteristic. Using the International Prognostic Scoring System (IPSS) Risk Group for MF patients, 5 patients (29%) were low risk, 9 patients (53%) were intermediate risk, and 2 patients (12%) were high risk. Eight patients (47%) developed MF post PV/ET. The mean baseline hemoglobin, leukocyte and platelet counts were similar amongst the MPN subgroups, likely representing the patients prior exposure to first-line therapies. Mean hemoglobin was 13.1 gm/dL, mean leukocyte count was 7.6×10^9/L, and the mean platelet count was 552×10^9/L. The most common prior therapies before initiation of PegIFN2a include hydroxyurea (63%), anagrelide (32%), non-pegylated interferon alpha (19%), and phlebotomy (10%).

Patients received subcutaneous PegIFN2a weekly with a median starting dose of 80 micrograms/week (mcg/wk) (range 22.5-180 mcg/wk). Median maximum dose was 90 mcg/wk (range 30-300 mcg/wk). After adjustments for adverse effects and response, median weekly dosage at last follow up was 90 mcg/wk (range 15-180 mcg/wk). Dosage reductions occurred in 7 patients (6%). A total of 87 patients (74%) remain on PegINF2a with a median duration of treatment of 17 months (1.0-92). Twenty patients (17%) discontinued therapy secondary to adverse effects.

Both hematologic and non-hematologic adverse effects (AE) were grade (Gr) 3 or lower (Table 2), with only 4 patients (3%) experiencing Gr 3 AEs. In the composite hematologic AE profile of all MPN patients analyzed (118), there were 7 patients who developed anemia (6%), 10 with thrombocytopenia (8%) and 7 with leukopenia (6%). Most common non-hematologic toxicities were Grade 1-3 fatigue in 24 patients (20%), Grade 1 liver function test (LFT) elevation in 7 (6%), and Grade 1-2 skin/allergic reaction in 6 (5%). Adverse effects leading to discontinuation were primarily non-hematologic, although one patient (<1%) discontinued PegIFN2a therapy due to Grade 2 anemia. Other reasons for discontinuation include participation in clinical trials, progression of disease and pregnancy. The percentage of discontinuation due to adverse effects in this study is consistent with the recently published French study in MF and a US study in PV and ET.[3,4]

Recently, standardized definitions were established to foster more objective assessment of treatment response. This analysis used all the standardized response definitions available, including the European Leukemia Net (ELN) criteria to measure response in PV and ET patients, the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) and European Myelofibrosis

Table 1. Clinical characteristics in 118 myeloproliferative neoplasm patients treated with pegylated interferon alpha 2a.

Characteristic	PV (n=55)	ET (n=46)	MF (n=17)
Age (years) Median	49 (22-64)	49 (16-64)	49 (38-72)
Sex Female	34 (62%)	30 (65%)	6 (35%)
Time from diagnosis (months) Median	44 (0-298)	44 (0-242)	44 (0-312)
Positive JAK2V617F	50 (91%)	17 (37%)	9 (53%)
Hemoglobin (gm/dL) Median	13.2 (11.4-19.2)	13.1 (8.1-17.6)	13.0 (8.3-14.6)
WBC (x10⁹/L) Median	8.0 (3.4-26.6)	7.5 (2.2-13.4)	7.4 (2.2-28.5)
Platelets (x10⁹/L) Median	544 (133-1645)	561 (174-1473)	552 (129-673)
Presence of splenomegaly	14 (25%)	6 (13%)	8 (47%)
Median n. of prior therapies	1 (range 0-4)	2 (range 0-4)	2 (range 0-5)
International Prognostic Scoring System (IPSS) Risk Group	NA	NA	Low: 5 (29%) Intermediate: 9 (53%) High: 2 (12%) Unknown: 1 (6%)
Post PV/ET	NA	NA	8 (47%)

Table 2. Adverse effects in 118 MPN patients treated with PegIFN2a.

	Number with adverse effect (# patients, % total)	Grade 3 adverse effect (# patients, % total)	Adverse effect leading to discontinuation (# patients, % total)
Hematologic			
Thrombocytopenia	10 (8%)	-	
Anemia	7 (6%)	-	1 (5%)
Leukopenia	7 (6%)	-	
Non-hematologic			
Fatigue	24 (20%)	1 (25%)	6 (30%)
LFT elevation	7 (6%)	-	
Skin/allergic reaction	6 (5%)	-	3 (15%)
Nausea	5 (4%)	-	
Mood disorder	5 (4%)	-	1 (5%)
Headache	3 (2.5%)	-	3 (15%)
Alopecia	3 (2.5%)		1 (5%)
Myalgias	3 (2.5%)	1 (25%)	2 (10%)
Stomatitis	2 (2%)	1 (25%)	2 (10%)
Thyrioditis	1 (<1%)	1 (25%)	
Cough	1 (<1%)		1 (5%)

Table 3. Response assessment in 118 myeloproliferative neoplasm patients treated with pegylated interferon alpha-2a.

Criteria	PV (n=55)	ET (n=46)	MF (n=17)
ELN	30 CR (54%) 18 PR (33%) 4 NR (7%) 3 NA (5%)	29 CR (63%) 7 PR (15%) 4 NR (9%) 6 NA (13%)	N/A
IWG-MRT			2 PR (12%) 3 CI (18%) 7 SD (41%) 4 NA (23%) 1 OC (6%)
EUMNET			1 CR (6%) 4 MaR (24%) 3 MoR (18%) 1 MiR (6%) 2 NR (12%) 4 NA (24%) 2 OC (12%)

**ELN Criteria.[8] CR-Complete response: platelet count less than or equal to 400×10⁹/L, no disease-related symptoms, normal spleen size, and white blood cell count less than or equal to 10×10⁹/L. PR-Partial response: platelet count less than or equal to 600×10⁹/L or a decrease greater than 50% from baseline. NR-No response: any response that did not satisfy PR criteria.*

**IWG Criteria.[9,10] CR: complete remission; PR: partial remission; CI: clinical improvement; PD: progressive disease; SD: stable disease. Relapse(see reference for full explanation of criteria).*

**EUMNET Criteria.[9,10] CR: complete response; MaR: major response; MoR: moderate response; MiR: minor response; NR: no response; Histologic response; Cytogenetic response (see reference for full explanation of criteria). NA: lost to follow up or too early to evaluate for response. OC: other criteria used.*

Network (EUMNET) criteria sets to evaluate response in MF patients (Table 3). According to ELN criteria, a complete response (CR) or partial response (PR) was observed in 30 (54%) and 18 (33%) PV patients treated with PegINF2a, respectively. In ET, 29 patients (63%) had CR while 7 (15%) experienced PR. Modest but useful rates of response were seen in MF patients. According to IWG-MRT criteria there were no complete remissions (CR); however, 2 patients (12%) had partial remission (PR), 3 had clinical improvement (CI) (18%), and 7 patients (41%) had stable disease (SD). According to EUMNET criteria, one MF patient had complete response (CR) (6%), 4 patients (24%) had major response (MaR), and 3 patients (18%) had minor response (MiR). In the overall cohort with splenomegaly (28 patients), 19 patients (68%) experienced a reduction in spleen size (cm) as measured below costal margin on clinical examination, with a mean 82% reduction in spleen size.

The Philadelphia negative MPNs are associated with substantial vascular and transformative sequelae. Unlike their BCR-ABL positive counterparts, medications that are both cytoreductive and possess the ability to induce molecular remissions have been elusive in the treatment of MPNs. The enhanced tolerability of the pegylated formulation of IFN2a in conjunction with significant hematologic and molecular remission rates makes it an attractive second-line agent. Whether it is preferable to HU as first-line therapy deserves consideration. Furthermore, Jak-2 inhibitors are now approved for advanced MF. The role of Jak-2 inhibition in early MF, PV and ET is the subject of ongoing study and may play a role complementary to that of PegIFN2a.

This study is limited by its retrospective nature, possible selection bias, and lack of standardized assessment of adverse events; however, use of PegIFN2a in these MPNs was associated with similar response rates, discontinuation rates, and adverse event profile, as previously reported in clinical trials. Although not quantitated in this analysis, additional benefit from PegIFN2a may be related to its ability to induce molecular remissions, as shown in previous phase II studies. Recent data support Jak-2 allelic burden as being associated with more aggressive and symptomatic manifestations amongst MPNs, as reflected by higher hematocrits, leukocyte counts, LDH and alkaline phosphatase values in those with elevated levels of *Jak-2V617F* RNA.[11-12] Jak-2 mutational status is also a known factor associated with risk of vascular events.[13] The relationship of allele burden to thrombotic events, which were not recorded in this study, deserves further investigation.

In conclusion, PegIFN2a is a non-leukemogenic therapy that possesses the ability to induce both hematologic and molecular remissions in MPNs and may be an agent of particular interest in the treatment of real world patients who have failed prior therapies or in those with early MF with the intent to hinder progression to overt MF.

From the experience of the collaborative investigators in this study, a starting dose of PegIFN2a at 45 mcg weekly titrated to a goal dosage of 90 mcg weekly is suggested as the optimal dosing strategy to limit AEs and maximize response. Upcoming randomized clinical trials through the Myeloproliferative Disorders Research Consortium will help further define the role of Peg IFN2a in MPNs.

Authorship and Disclosures

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