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Pegylated interferon alpha – 2a is clinically effective and tolerable in myeloproliferative neoplasm patients treated off clinical trial

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ABSTRACT

Polycythemia vera, essential thrombocytosis, and myelofibrosis are chronic Philadelphia-negative myeloproliferative neoplasms that are characterized by clonal hematopoiesis, splenomegaly, risk of hemorrhagic and thrombotic sequelae, and profound symptom burden. We review the outcomes of 75 myeloproliferative neoplasm patients treated with pegylated interferon alpha 2a off study at an academic medical center. In the 56 treated polycythemia vera and essential thrombocytosis patients, a complete or partial response was obtained in 78.6% of patients per ELN/IWG-MRT revised criteria, with >80% of polycythemia vera patients becoming phlebotomy independent and 60% of essential thrombocytosis patients having platelet normalization with therapy. In the 19 treated myelofibrosis patients, stable disease was seen in 63.2% of patients. Vascular events occurred in 2/75 (2.6%) of treated patients while on therapy. Grade 3 toxicity was uncommon with leukopenia noted in 1 patient (1.3%). The most common adverse event overall was grade 1 fatigue in 18.7%. This retrospective single center analysis demonstrates pegylated interferon alpha 2a is active and well-tolerated therapy outside the support of a clinical trial. These results substantiate the previously reported efficacy of pegylated interferon alpha 2a in myeloproliferative neoplasms. Further prospective and randomized clinical trial data is required to better delineate pegylated interferon alpha 2a's use in myeloproliferative disease, with emphasis placed on comprehensive molecular characterization, allelic burden quantification, and measurement of histologic response.

1. Introduction

Polycythemia vera (PV), essential thrombocytosis (ET), and myelofibrosis (MF) are chronic Philadelphia-negative myeloproliferative neoplasms (MPNs) that are characterized by clonal hematopoiesis, splenomegaly, risk of hemorrhagic and thrombotic sequelae, and profound symptom burdens [1,2]. The discovery of the JAK*V617F* somatic mutation and the subsequent constitutively active tyrosine kinase activity has led to a therapeutic revolution in the treatment of MPNs. Ruxolitinib, an orally available JAK inhibitor, has led to reductions in splenomegaly, improved symptom burden, and improvement in overall survival [3–6]. Despite this, treatment of MPNs continues to be a challenge secondary to dose limiting cytopenias associated with JAK inhibition [7–9]. Interferon alpha 2a (IFNα2a) has been of clinical interest in MPNs for over two decades and was noted to be an effective agent for cytoreduction [10,11]. Although early interferon therapy was associated clinical efficacy, it's significant toxicity profile restricted its clinical utility. Later, the introduction of pegylated interferon α2a (peg IFN α2a) presented a more tolerable and convenient form of interferon therapy and restored interest in its use for the treatment of MPN patients. Peg IFN α2a was subsequently shown in clinical trials to induce clinical, hematologic, molecular, and histologic responses in treated MPN patients [12–17]. Additionally, the expected enhanced tolerability of pegylated interferon was confirmed in an international multicenter retrospective analysis [18]. Interestingly, Peg IFN α2a has therapeutic effects beyond cytoreduction including decrease in *JAKV617F* mutational (allelic) burden and reduction in marrow fibrosis indicating that it may targeting the MPN progenitor and stem cells [19–22]. Momentum for peg IFN α2a therapy in the treatment of MPN patients continues to build with many ongoing clinical trials (clinicaltrials.gov NCT00452034, NCT01259817, NCT02218047, NCT01259856). Here we discuss outcomes of MPN patients treated with peg IFN α2a seen outside of a clinical trial setting at an academic medical center.

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2. Methods

Patients treated with peg IFN α2a outside a clinical trial between the years 2006 and 2015 were identified at Mayo Clinic, Scottsdale. Charts were reviewed retrospectively, using the electronic medical records, for demographic and clinical data. Toxicity to therapy was assessed using the CTCAE 4.0 criteria. Therapeutic responses for ET and PV were calculated by the revised ELN/IWG-MRT criteria including complete remission (CR), partial remission (PR), no response (NR), or progressive disease (PD) [23]. Responses in MF were calculated by both the a) EUMNET criteria [24] including complete response (CR), major response (MR), moderate response (MoR), minor response (MiR) and NR and b) by revised IWG-MRT/ELN criteria [25] including CR, PR, clinical improvement (CI), stable disease (SD) or PD. Best response over all cycles of treatment was assessed. Overall response rate (ORR) for ET and PV was considered to be a best response of CR or PR. For MF, ORR was considered to be CI or PR (ELN IWG criteria) or CR, MR, MoR and MiR (Eunmet criteria) for best response. 95% confidence intervals for ORR were constructed. Spleen response was measured on physical exam as centimeters below the costal margin by the treating hematologist. Follow up was provider dependent with general clinical practice being a follow up visit monthly with complete blood count and chemistry panel. Thyroid function evaluation was generally performed at baseline, at 3 months, or if clinically indicated sooner or more frequently. Baseline eye exams were performed in some patients but not all. Molecular data was limited to JAK *V617F*. The study was approved by the institutional review board and was in keeping with the Declaration of Helsinki and federal regulations (HIPAA).

3. Results

3.1. Patients

Seventy five MPN patients treated with pegylated interferon outside of a clinical trial setting between the years 2006 and 2015 were identified. There were 36 PV patients (48%), 20 ET patients (26.7%), and 19 MF patients (25.6%). Thirteen MF patients were post-PV/ET MF. The median age at diagnosis was 51.5 yrs (range 28.8–75.1). JAK2 *V617* mutation was present in 53 patients (70.7%). PV risk scores [27] (n = 36) include: Low in 10 (27.7%), Intermediate in 18 (50%), High in 7 (19.4%) and unknown in 1 (2.7%). For patient with ET (n = 20) IPSET [28] risk scores include: Low in 12 (60%), Intermediate in 6 (30%), and high in 2 (10%). DIPSS risk category [26] for the 19 MF patients: Low in 6 (31.5%), Intermediate-1 in 3 (15.7%), Intermediate-2 in 8 (42%), and High in 2 (10.5%) patients. Overall, the majority of patients (82.2%) had received at least one prior cytoreductive therapy for their disease. Other demographic and disease characteristics are outlined in Table 1.

Table 1
Demographic and disease characteristics of 75 MPN Patients on Peg IFN α2A.

Characteristics	Number of patients (%)
Gender:	39 (52%)
Female	36 (48%)
Male	
Median age at diagnosis in years (range)	51.5 (28.8–75.1)
Diagnosis:	36 (48%)
PV	20 (26.7%)
ET	19 (25.6%)
MF	
JAK2 V617 mutation	53 (70.7%)
Prior therapies included:	54 (72%)
Hydroxyurea	25 (33.3%)
Phlebotomy	24 (32%)
Anagrelide	
DIPSS [26] prognostic score (MF patients = 19):	6 (31.5%)
Low	3 (31.5%)
Intermediate-1	8 (42%)
Intermediate-2	2 (15.7%)
High	
PV Risk Score [27] (PV patients = 36):	10 (27.7%)
Low	18 (50%)
Intermediate	7 (19.4%)
High	1 (2.8)
Unknown	
ET IPSET[28] Risk Score (ET patients = 20):	12 (60%)
Low	6 (30%)
Intermediate	2 (10%)
High	

Table 2
Toxicity.

TOXICITY			
Hematological toxicity (N = 75)			
	Grade 1, n (%)	*Grade 2, n (%)*	*Grade ¾, n (%)*
Leukopenia	13 (17.3)	5 (6.7)	1 (1.3)
Anemia	10 (13.3)	1 (1.3)	0
Thrombocytopenia	13 (17.3)	1 (1.3)	0
Non-hematological toxicity (N = 75)			
	Grade 1, n (%)	*Grade 2, n (%)*	*Grade ¾, n (%)*
Fatigue	14 (18.7)	4 (5.3)	0
Transaminitis	6 (8)	3 (4)	0
Myalgias	4 (5.3)	0	0

3.2. Therapy

Median starting dose of peg IFN α2a was 45 micrograms/week via self-injection from peg IFN α2a vials (range, 45–90 mg/week). The median peak dose was 90 mg/week (range, 45–270 mg/week). Peg IFN α2a was tolerated at a median dose of 60 mg/week (range 5.6–180 mg/week). Treatment was pursued for a median duration of 24 months (range, 3.6–85 months). Median follow up was 3.8 years (range, 1 month–8.7 years).

3.3. Tolerability

Specific toxicities to therapy were assessed per CTCAE 4.0 criteria (see Table 2). Hematological toxicity included: leukopenia at grade 1 in 13 patients (17.3%), grade 2 in 5 patients (6.7%), and grade 3 in 1 patient (1.3%), anemia at grade 1 in 10 patients (13.3%) and grade 2 in 1 patient (1.3%), thrombocytopenia at grade 1 in 13 patients (17.3%) and grade 2 in 1 patient (1.3%). The most common non-hematologic toxicity included: fatigue at grade 1 in 14 patients (18.7%) and grade 2 in 4 patients (5.3%), transaminitis at grade 1 in 6 patients (8%) and grade 2 in 3 patients (4%), myalgias at grade 1 in 4 patients (5.3%), grade 2 myalgias in 3 patients (4%), grade 1 mood changes in 2 patients (2.6%), grade 2 rash and grade 2 sensory neuropathy in 1 patient (1.3%) each. Thirty two patients discontinued therapy secondary to: treatment associated adverse events in 14 patients (43.7%), progression of disease or lack of response in 13 patients (40.6%), patient preference for alternate therapy or treatment break in 3 patients (9.3%), and insurance complications in 2 patients (6.2%).

3.4. Response

3.4.1. ELN/IWG-MRT criteria

In the PV/ET group 56 patients were evaluated by ELN/IWG-MRT criteria. Overall, a response was seen in 44 (78.6%; 95% CI: 65.6–88.4%) patients. A complete remission (CR) was seen in 8 patients (14.3%; 95% CI: 6.4–26.2%), a partial remission (PR) in 18 patients (32.1%; 95% CI:20.3–46.0%), either a CR or PR in 18 patients (32.1%; 95% CI: 20.3–46.0%) (when histologic remissions