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A Real World Study: Efficacy and Safety of Pegylated Interferon Alpha-2a in Patients with Myeloproliferative Neoplasm

Gerçek Yaşam Çalışması: Miyeloproliferatif Neoplazm Hastalarında Pegile İnterferon Alfa-2a'nın Etkinliği ve Güvenliği

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Abstract

Objectives: Several clinical studies have reported promising results in patients with essential thrombocythemia (ET) and polycythemia vera (PV) treated with pegylated interferon alpha-2a (PEG-IFN-α-2a). In this study, we evaluated the efficacy and safety of PEG-IFN-α-2a in patients with myeloproliferative neoplasms (MPNs) followed and treated in our clinic.

Materials and Methods: In this retrospective analysis, we present the outcomes of 39 patients diagnosed with MPNs (25 with ET, 13 with PV, 1 with primary myelofibrosis) who received PEG-IFN-α-2a between 2014 and 2021.

Results: The average age of the participants was 49 years, ranging from 23 to 71. Most patients (92%) had received at least one prior cytoreductive therapy. The median starting dose of PEG-IFN-α-2a was 126 mcg/week (range, 22.5-180 mcg/week), administered by self-injection. The median duration of treatment was 24 months (range, 1-77). The overall response rates in patients with PV and ET were 84.6% and 92%, respectively. The most common adverse events observed during the treatment period were fatigue (71%), myalgia (54%), and arthralgia (53%).

Conclusion: Our results suggest that PEG-IFN-α-2a remains a feasible treatment option, particularly for younger patients who wish to avoid prolonged cytotoxic therapy.

Keywords: Pegylated interferon alpha-2a, polycythemia vera, essential thrombocythemia

Öz

Amaç: Bazı klinik çalışmalarda, pegile interferon alfa-2a (PEG-IFN-α-2a) ile tedavi edilen esansiyel trombositemi (ET) ve polisitemia vera (PV) hastalarında umut verici sonuçlar bildirmiştir. Biz de bu çalışmada, kendi kliniğimizde takip ve tedavi ettiğimiz miyeloproliferatif neoplazm (MPN) tanılı hastalarımızda PEG-IFN-α-2a etkinlik ve güvenilirliğini değerlendirdik.

Gereç ve Yöntem: Bu retrospektif analizde, 2014 ve 2021 yılları arasında tanı almış ve PEG-IFN-α-2a ile tedavi edilmiş, 39 MPN tanılı hastanın (25 ET, 13 PV, 1 primer miyelofibrozis) sonuçlarını sunduk.

Bulgular: Hastaların ortanca yaşı 49 (aralık, 23-71) olup, çoğunluğu (%92) daha önce en az bir sıra farklı sitoredüktif tedaviyi almıştı. PEG-IFN-α-2a'nın ortanca başlangıç dozu 126 mcg/hafta (aralık, 22,5-180 mcg/hafta) olup, hastalar tedaviyi kendine-enjeksiyon ile uygulanmıştır. Hastalar ortanca 24 ay (aralık, 1-77) tedavi almıştır. Polisitemi vera ve ET tanılı hastalarda tüm yanıt oranları sırasıyla %84,6 ve %92 olarak bulunmuştur. Tüm hastalar arasında tedavi süresinde gözlemlenen en yaygın yan etkiler yorgunluk (%71), miyalji (%54) ve artralji (%53) olmuştur.

Sonuç: Sonuçlarımız, PEG-IFN-α-2a'nın, özellikle uzun süreli sitotoksik tedaviden kaçınmak isteyen daha genç hastalar için uygulanabilir bir tedavi seçeneği olabileceğini göstermektedir.

Anahtar Kelimeler: Pegile interferon alfa-2a, polisitemia vera, esansiyel trombositemi

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Introduction

BCR-ABL negative myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are clonal hematopoietic disorders. They are noted for thrombohemorrhagic sequelae, splenomegaly and the potential for transformation to secondary myelofibrosis, acute leukaemia or myelodysplasia (1,2). Cytoreductive therapy (typically with hydroxyurea) initiation is strongly indicated for high-risk ET and PV patients to extenuate the risk of thrombosis (1,2).

Interferon alpha (IFN-α) has been attainable over three decades and is used for treatment various cancers. Among the limited therapeutic options for MPNs, interferons continue to envolve. Nowadays, IFN has been the actual cornerstone of MPNs treatment via antiproliferative, proapoptotic, antiangiogenic and immunomodulatory effects (3). Through declared mechanisms, IFN-α depletes MPNs clones and direct apoptotic effect on hematopoietic progenitors (4). However therapeutic benefits, interferons have limited use for side effect profile and public regulatory approval difficulty.

Recently, interferons gain center of attention again with recombinant long-acting pegylated forms. Pegylated interferons (PEG-IFNs) have improved tolerability with more convenience, less-frequent injection intervals and better side effects profiles. Among all, PEG-IFN-α-2a has achieved meaningfull clinical-hematological as well as molecular and histological responses in several studies (5-8). Herein, we analyze the outcomes of PEG-IFN-α-2a theraphy in patients with MPNs at our centre.

Materials and Methods

Patients received PEG-IFN-α-2a (Pegasys, Roche) at our centre were enrolled in the study. Philadelphia chromosome-negative [Ph(-)] MPNs were identified in accordance with the World Health Organization 2008-2016 criteria. Relevant clinical data were collected from the hospital medical record system retrospectively. The participants were called-up or visited face-to-face to check data accuracy. The large majority of individuals had previously been exposed to at least one cytoreductive agent, with the exception of an off-label first-line use of PEG-IFN-α-2a.

Defination of hydroxyurea resistance/intolerance includes; insufficient depletion (platelet count >600×10^9/L; hematocrit (HCT) >45%; or continuing phlebotomy necessity; or leucocyte >10×10^9/L), progressive splenomegaly in spite of 3 months hydroxyurea ≥2 g/day or occurrence hematological or non-hematological toxicities at any dose (9).

Most patients received PEG-IFN-α-2a via subcutaneous injection once a week at a starting dose of 90 mcg. Other dosing schemes were administered to obtain appropriate response (eg, 90 µg biweekly or monthly). The dose and injection intervals were changed due to on toxicity or insufficient efficacy. The administration of treatment was continued until the patients demonstrated clinically meaningful benefits.

Regular assessments of peripheral blood tests and size of spleen through physical exams were performed at baseline and follow-up visits every 2 to 6 months. The European Leukemia Net (ELN)/International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria were employed to assess the hematological responses of patients with PV and ET (10). Complete hematologic response (CHR) was characterised by normalisation of blood parameters (ET: platelets ≤400x10^9/L; PV: HCT <45% without phlebotomy, platelets ≤400x10^9/L; ET/PV leucocyte <10x10^9/L) with complete disappearance of palpable or imaging splenomegaly/symptoms without thrombotic event. A partial hematologic response (PHR) was defined as a 50% or greater reduction in the platelet count for ET or a reduction in phlebotomy by ≥ 50% or a reduction in spleen size as palpated or imaged by ≥50% in PV (10). The European Myelofibrosis Network (EUMNET)/IWG-MRT criteria were employed to determine the response in patients with MF (11,12).

The analysis of bone marrow histomorphologic data and *JAK2V617F* gene mutation was limited (10,13). Molecular complete remission (CR) required undetectable JAK2V617F levels; PR required ≥50% reduction from baseline (existing at least %20 mutant allele burden) (10,13). Only patients with a detectable JAK2V61F mutation at baseline were assessed for molecular response.

The proportion of severe adverse events was calculated. Thyroid and liver function tests were evaluated for all the participants. Data on the reduction in the need for phlebotomies, and the history of thrombotic and haemorrhagic events before and after therapy were collected. Common Terminology Criteria for Adverse Events (CTCAEs) (version 4.0) was used to classify all AEs. The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (date: 10.12.2021, approval no.: İ10-663-21).

Statistical Analysis

For continuous variables, the median (minimum-maximum) or interquartile range (IQR) was given. Categorical variables were presented as frequencies. Response was analysed using the intention-to-treat method. A response rate of ≥35% was considered to indicate efficacy and justify larger studies. Best responses treatment cycles were evaluated. Overall response rates (ORRs) are presented with 95% confidence intervals (CIs). A logistic regression analysis was performed to determine any relationship between CHR and patient demographic, clinical

characteristics, with adjusted odds ratios. SPSS v.20 was used for all analyses.

Results

Patients

A total of 39 patients were included in the study between 2014-2021 (PV, 13; ET, 25; MF,1). The median age of the participants was 49 years (range, 23 to 71). Eight patients (21%) were older than 60 years. The median duration from diagnosis was 52 months (range, 0-269). JAK2V617F mutation was present in 15 patients (41%). At least one previous cytoreductive treatment was given to 92% of patients. Twelve (92%) of 13 patients were resistant or intolerant to hydroxyurea (alone or with anagrelide). The vast majority of patients (87%) had a severe adverse effect of interferon. Additional demographic and clinical features are shown in Table 1.

Therapy

Patients administered PEG-IFN-α-2a for a median of 24 months (range, 1 to 77) at a median initial dose of 126 micrograms/week (mcg/wk) (range, 22.5 to 180). Of all patients studied, 7 (18%) had a dose reduction and 2 (5%) had an escalation of the dose of PEG-IFN-α-2a to achieve the optimal therapeutic benefit. After dose adjustments, the median maximum dose was 135 mcg/wk (range, 22.5-180). At last follow-up, the median dose of PEG-IFN-α-2a was 94.5 mcg/wk (range, 22.5-180).

Reasons for treatment discontinuation were treatment-emergent AEs (n=7, 39%), achieving a durable response (n=4, 22%), skip routine medical check-up due to coronavirus disease-2019 (COVID-19) pandemic (n=3, 17%), pregnancy (n=2, 11%), disease progression (n=1, 5.5 %) and death (n=1, 5.5%). The median follow-up period was 28 months (range, 1-77). At time of analysis 21 (54%) patients were still actively receiving the therapy.

Table 1: Demographic and disease characteristic of myeloproliferative neoplasm patients on PEG-IFN-α-2a

Characteristic	PV (n=13)	ET (n=25)	MF (n=1)	Total (n=39)
Median age	33 (17-57)	38 (20-61)	54	35 (17-61)
Males, n (%)	8 (62)	8 (32)	0	16 (41)
Females, n (%)	5 (38)	17 (68)	1 (100)	23 (59)
Time from diagnosis to initiation of PEG-IFN-α-2a, months	62 (21-125)	44 (0-269)	0	52 (0-269)
<3 years, n (%)	2/13 (15)	12/25 (48)	0	15/39 (38)
3-5 years, n (%)	4/13 (31)	3/25 (12)	0	7/39 (18)
≥5 years, n (%)	7/13 (54)	10/25 (40)	0	17/39 (44)
JAK2V617F-positive (%)	7/11 (64)	7/25 (28)	1/1 (100)	15/37 (41)
Median white blood cell count, $\times10^9$ /L	7.8 (4-24)	9.5 (2.7-15.4)	8.1	8.52 (2.7-24)
White blood cell count ≥11×10^9 /L, n (%)	3 (23)	5 (20)	0	8 (21)
Median hemoglobin, g/dL	16.1 (13.5-18.5)	12.6 (9-16.6)	13.5	13.6 (9-18.5)
Median haematocrit value	48.9 (43.7-57)	41.1 (26.6-53.1)	42.6	43 (26.6-57)
Median platelet count, $X10^9$ /L	246 (174-1080)	773 (367-1582)	280	614 (174-1582)
Platelet count ≥1000×10^9, n (%)	1 (8)	5 (20)	0	6 (15)
Bone marrow results				
Fibrosis grade 0, n (%)	1/9 (11)	2/24 (8.5)	0	3/34 (9)
Fibrosis grade 1, n (%)	4/9 (45)	11/24(46)	1/1(100)	16/34 (47)
Fibrosis grade 2, n (%)	3/9 (33)	8/24 (33)	0	11/34 (32)
Fibrosis grade 3, n (%)	1/9 (11)	2/24 (8.5)	0	2/34 (6)
Fibrosis grade 4, n (%)	0	1/24 (4)	0	1/34 (3)
Suboptimal, n (%)	0	0	0	1/34 (3)
Blasts, n (%)	0	0	0	0
Significant splenomegaly, n (%)	7/13 (46.7)	8/25 (53.3)	0/1 (0)	15/39 (38.4)
Splenectomy, n (%)	0	1/25 (4)*	0	1/39 (3)
Median number of prior therapies	2 (1-3)	2 (0-3)	1	2 (0-3)

Table 1: Continued				
Characteristic	**PV (n=13)**	**ET (n=25)**	**MF (n=1)**	**Total (n=39)**
Prior therapy				
Phlebotomy, n (%)	12/13 (92.3)	3/25 (12)	0/1 (0)	15/39 (38.4)
Hydroxyurea, n (%)	11/13 (85)	21/25 (84)	1/1(100)	33/39 (85)
Anagrelide, n (%)	0	13/25 (52)	0	13/39 (33)
Hydroxyurea alone, n (%)	5/13 (38)	3/25 (12)	1/1(100)	9/39 (23)
Hydroxyurea+anagrelide, n (%)	0	4/25 (16)	0	4/39 (10)
Interferon alfa, n (%)	7/13 (54)	16/25 (64)	0	23/39 (59)
Interferon alfa alone, n (%)	1/13 (8)	0	0	1/39 (3)
Hydroxyurea+interferon alfa, n (%)	6/13 (46)	7/25 (28)	0	13/39 (33)
Anagrelide+interferon alfa, n (%)	0	2/25 (8)	0	2/39 (5)
Hydroxyurea+anagrelide+interferon alfa, n (%)	0	7/25 (28)	0	7/39 (18)
Previously untreated, n (%)	1/13 (8)	2/25 (8)	0	3/39 (8)
Causes of hydroxyurea discontinued (alone or with anagrelide)				
Resistant/ intolerant, n (%)	5/13 (38)	7/25 (28)	0	0
N/A, n (%)	-	-	1(100)	-
Causes of interferon discontinued (alone or with hydroxyurea, anagrelide or both)				
Severe AEs, n (%)	6/7 (86)	13/16 (81.25)	-	19/23 (83)
Interferon absence	1/7 (14)	2/16 (13)	-	3/23 (13)
Decrease enjection of IFN frequency	0	1/16 (6.25)	-	1/23 (4)
History of major thrombosis, n (%)	1/13 (8) Mesenteric ischemia-ACVD (1)	6/25 (24) PE (1) ACVD (1) PVT-ACVD (1) CVA (2) Venous trombosis in leg (1)	1/1 (100) PE (1)	8/39 (21)

*Before PEG-IFN 2A theraphy, PE: Pulmonary thromboembolism, ACVD: Atherosclerotic heart disease, CVA: Cerebrovascular accident, PVT: Portal vein thrombosis, N/A: Non-applicable, AEs: Advers effect, PV: Polycythemia vera, ET: Essential thrombocythemia, PEG-IFN-α-2a: Pegylated interferon alpha-2a

Toxicity

During the PEG-IFN-α-2a therapy, 92% (34/37) of patients experienced at least one AE, but most of these were grade 1 or 2. The most frequent AEs were fatigue (71%), myalgia (54%), arthralgia (53%), headache (50%), dizziness (38%) and flu-like symptoms (32%).

Nineteen percent (7) of patients experienced grade 3-4 AEs, including elevated liver function tests (n=2), hyperthyroidism (n=2), Hashimoto thyroiditis (n=1) and others (n=2) listed in Table 2. Withdrawal from treatment occurred in all of them. One patient resumed treatment after seven months with the with recovery of thyroid function. The profile of hematological AEs in all patients was grade 1-2 (Table 2). One patient discontinued treatment for one month due to grade 2 thrombocytopenia. All adverse effects were dose independent.

Response

Hematological Response

Thirty-seven patients were evaluable for response. In PV patients, 1 (8%) had a CR and 10 (77%) had a PR, resulting in an ORR of 84.6% (95% CI 82.9-86.7%). In the ET cohort, CR and PR were reported in 9 (36%) and 14 (56%) patients, respectively resulting in an ORR of 92% (95% CI 90.7-93.8%). The best ORR at any time point of theraphy was 92.3% (95% CI 91.1-94.2%) for PV patients and 96% (95% CI 95-97.4%) for ET patients. One patient with MF responded CR by EUMNET criteria and N/A by IWG-MRT criteria. Most responses were achieved within the first 3 months of treatment.

A total of 13 patients lost response (5 PV, 8 ET); nine patients due to disease progression (4 PV, 5 ET; from CR to PR); three patients after dose reduction or discontinuation due to COVID-19 pandemic or achievement of CR (1 PV, 2 ET); transformation to myelofibrosis in one patient with ET. The median time to response was 15 months (IQR, 9-24). Overall responses were still ongoing except for two patients. During the follow-up period, five patients discontinued PEG-IFN-α-2a. Four of the five patients were resumed PEG-IFN-α-2a after a median of 23 months (IQR, 12-39). Achieving a CR was not associated with age, gender, JAK2V617F allele burden, number of prior therapies, or bone marrow fibrosis grade (Table 3).

Table 2: Adverse events occurring in myeloproliferative neoplasms patients						
	PV (n=13)		ET (n=25)		MF (n=1)	
	All grades	Grade 3+	All grades	Grade 3+	All grades	Grade 3+
Hematologic						
Anemia	-	-	2 (8)	-	-	-
Lymphocytopenia	-	-	1 (4)	-	-	-
Thrombocytopenia	1(8)	-	1 (4)	-	-	-
Non-hematologic						
Abdominal pain	-	-	1 (4)	-	1 (100)	-
Alanine aminotransferase	3 (23)	2 (15)	2 (8)	-	-	-
Alopecia	3 (23)	-	6 (24)	-	1 (100)	-
Arthralgia	6 (46)	-	11 (44)	-	1 (100)	1 (100)
Bone pain	2 (15)	-	-	-	-	-
Cough	2 (15)	-	1 (4)	-	-	-
Cramp	2 (15)	-	2 (8)	-	-	-
Depression	2 (15)	-	3 (12)	-	1 (100)	-
Diarrhea	-	-	-	-	1 (100)	-
Dizziness	4 (31)	1 (8)	8 (32)	-	1 (100)	1 (100)
Edema	-	-	1 (4)	-	-	-
Epistaxis	1 (8)	-	1 (4)	-	-	-
Fatigue	10 (77)	1 (8)	13 (52)	-	1 (100)	1 (100)
Fever	3 (23)	1 (8)	3 (12)	-	1 (100)	1 (100)
Flulike symptoms	5 (38)	1 (8)	6 (24)	-	-	-
Headache	6 (46)	-	10 (40)	-	1 (100)	1 (100)
Injection site reaction	2 (15)	-	8 (32)	-	-	-
Insomnia	2 (15)	-	1 (4)	-	1 (100)	1 (100)
Irritability	1 (8)	-	6 (24)	-	1 (100)	-
Lack of appetite	2 (15)	-	1 (4)	-	1 (100)	1 (100)
Mood disorder	1 (8)	-	-	-	-	-
Myalgia	8 (62)	-	10 (40)	-	1 (100)	1 (100)
Mucositis and oral aphthae	1 (8)	-	-	-	1 (100)	-
Pruritus	1 (8)	-	4 (16)	-	1 (100)	1 (100)
Skin redness	-	-	1 (4)	-	-	-
Dry skin	-	-	1 (4)	-	-	-
Swelter	1 (8)	-	1 (4)	-	1 (100)	1 (100)
Thyrioditis	1(8)	-	2 (8)	2 (8)	-	-
Hypothyrodism	-	-	1 (4)	-	-	-
Hyperthyroidism	1 (8)	1(8)	-	-	-	-
Ecchymose	-	-	1 (4)	-	-	-
Nausea and vomiting	2 (15)	-	1 (4)	-	1 (100)	1 (100)

Data was N/A in 2 patients. PV: Polycythemia vera, ET: Essential thrombocythemia, MF: Myelofibrosis

At the time of the most recent assessment, 2 out of 13 patients (15%) had achieved a HCT level below 45% (Figure 1). In patients with PV, 12 out of 13 (92%) were receiving phlebotomy.

The median phlebotomy frequency in the year prior to therapy initiation was 4 (range, 1-48). For these patients, reduction in median number of phlebotomies by 3 (range, 1-6) per year. In addition, 7 out of 12 (58.3%) patients became phlebotomy-independent with treatment. Of the 25 patients with ET 13 (52%) had platelet normalisation (<400x10^9/L). In 2 (8%) patients with ET, the platelet counts decreased by more than 50% without normalisation (Figure 2).

Table 3: Clinical factors and association with complete hematologic response			
Risk factors	**Events/patients, n (%)**	**OR (95% CI)**	**p-value**
Age (continuous)	-	1.05 (0.97-1.1)	p=0.2
Disease type PV ET	 1/9 (11) 9/24 (38)	 3.11 (0.2-40.3) -	 p=0.38
Gender Male Female	 3/12 (25) 7/21 (33)	 1.23 (0.19-7.8) -	 p=0.82
JAK2 mutation No Yes	 8/21 (38) 2/12 (17)	 0.31 (0.34-3) -	 p=0.31
Median dose PEG received, mg/wk	90 (23-180)	1.01 (0.98-1.03)	p=0.44
Prior therapy (continuous)	-	0.85 (0.3-2.4)	p=0.77
Prior thrombosis Yes No	 1/6 (17) 9/27 (33)	 2.43 (0.19-30.5) -	 p=0.49

CHR: Complete hematologic response, OR: Overall response, CI: Confidence intervals, PV: Polycythemia vera, ET: Essential thrombocythemia, PEG: Pegylated interferon

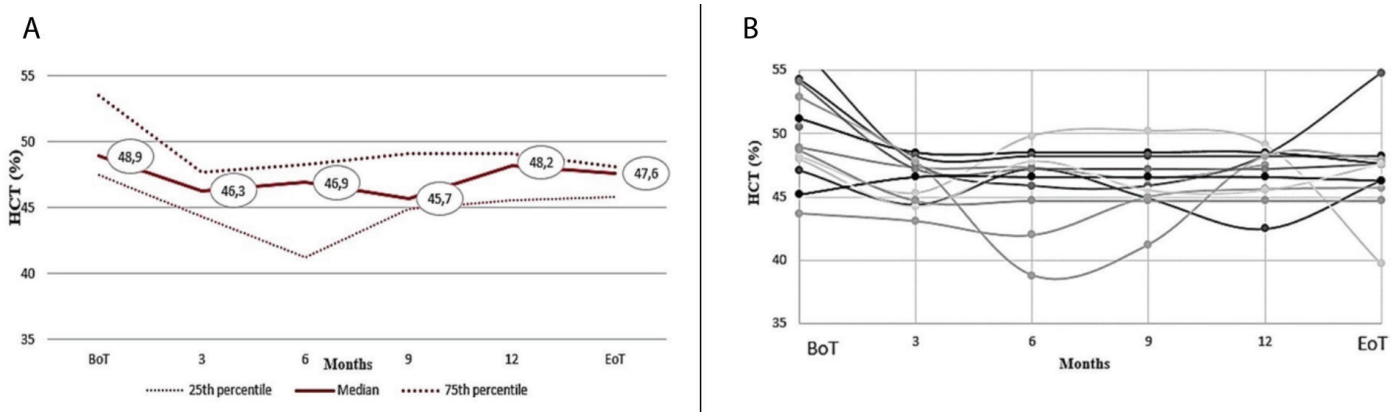

Figure 1: A) Hematocrit counts over time. Figure is shown the 25th, 50th (median) and 75th percentis for hematocrit count in patients with polycythemia vera. **B)** Hematocrit counts over time. Figure is shown the hematocrit counts in all paties with polycythemia vera

BoT: Beginning of treatment, EoT: End of treatment

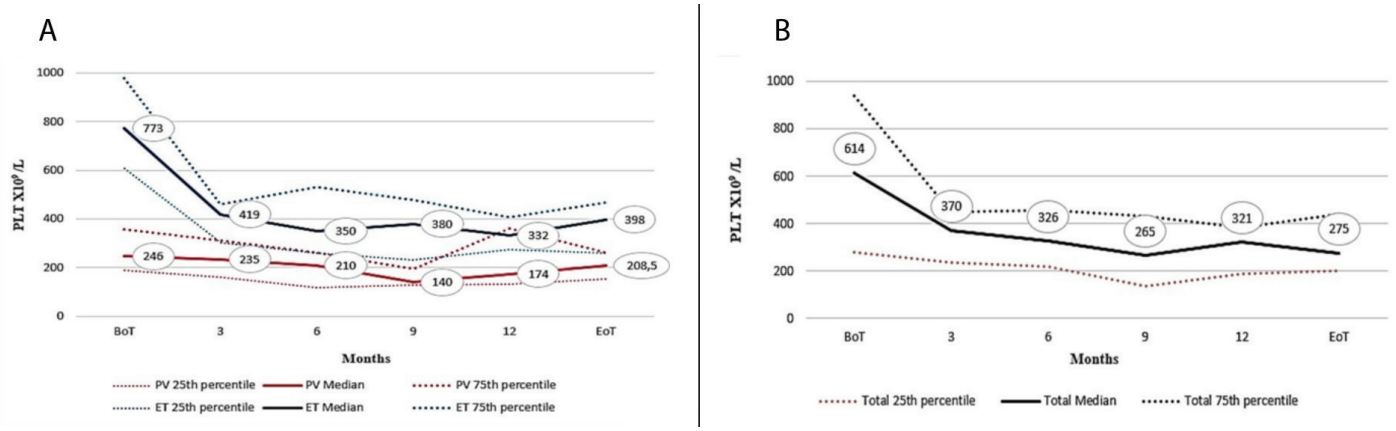

Figure 2: A) Platelet counts over time. Figure shown the 25th, 50th (median) and 75th percentis for platelet count in all patients. **B)** Platelet counts over time. Figure shown the 25th, 50th (median) and 75th percentis for platelet count in all patients with polycythemia vera and essential thrombocythemia

BoT: Beginning of treatment, EoT: End of treatment, PV: Polycythemia vera, ET: Essential thrombocythemia

Spleen Response

Of the 15 (38%) patients with palpable splenomegaly, 10 (66.7%) had a reduction of ≥5 cm. In 6 (60%) of these patients, the spleen became non-palpable.

Vascular Events

No haemorrhagic events occurred during therapy. One ET patient developed unprovoked vena femoralis thrombosis. The patient was 65 years old, had a 16-year medical history and had a PHR to 135 mcg/wk therapy within 38 months of follow-up.

Molecular and Histological Response

Molecular data was limited to JAK2V617F. Molecular response was assessable in 2 out of 7 (29%) ET patients with the JAK2V617F mutation. One achieved PR, with a JAK2V617F allele burden of 31% at baseline and 12.5-31% during follow-up. Other had a NR with stable allele burden in the range of 31-50%. A total of, 4 (10%) patients (2 PV, 2 ET) had a bone marrow response, including those with no response.

Discussion

In this study, we demonstrate that, PEG-IFN-α-2a is effective, safe and has a good tolerability in MPN patients. This analysis supports previous reports of significant clinicohematological and molecular activity also a reduction of phlebotomy, vasculer events related to PEG-IFN-α-2a. In addition, PEG-IFN-α-2a is better tolerated than IFN-α. Obviously, the benefit can be directly observed in patients discontinuing IFN-α due to severe side effects. Unlike some other studies, the majority of patients have exhausted therapeutic alternatives for the refractory nature of the disease, including an ORR of 84.6% in PV and 92% in ET patients.

Our analysis shows CHR rates of 8% and 36% in PV and ET patients, respectively, which are lower than in other studies (6,14-16). This may be due to longer disease duration. In total, 17 (44%) patients had been followed for at least 5 years before PEG-IFN-α-2a. Additionally, patients included in the study had an increased incidence of splenomegaly and vascular events. Impressively, CHR rates were observed in 38% of PV and 68% of ET patients with best response. Prolonged results from a phase 2 trial showed CHR and ORR in 75% and 80% respectively at first response, but 38% and 39% at last assessment (15). It is also important to note that the ORR in our study is higher than in this clinical trial, which may be explained by the different length of follow-up. Also, some de novo mutations, including those in e.g. DNMT3A, TET2, ASXL1,TP53, IDH1/2 have occurred during therapy, but are not targeted by PEG-IFN-α-2a (17,18). These mutant clones may contribute to the decline in response rates over time.

PEG-IFN-α-2a appeared to be well tolerated in most patients. More than two-thirds of MPN patients experienced more than one type of toxicity, even with low-doses of PEG-IFN-α-2a. The highest dose administration of 450 mcg/wk therapy was published by Quintas-Cardama et al. (6). In this study, the highest discontinuation rate was at doses above 180 mcg/wk. In our study, only 3 patients (8%) received the maximum dose of 180 mcg/wk. Therefore, our discontinuation rate was dose-independent. The overall discontinuation rate due to adverse events was 19%, which is consistent with the results of other studies with shorter follow-up (15,19,20). None of the patients required a dose reduction due to adverse events. These data suggest that the optimal dose of PEG-IFN-α-2a has not yet been established and the optimal balance between efficacy and tolerability is being investigated.

The most common grade 3-4 toxicities were liver enzyme elevations, dizziness, fatigue, fever and thyroiditis in two patients each (5%). We have reported some rare adverse events here, that may not have been reported in other studies (e.g. dry skin, ecchymosis, epistaxis, irritability, loss of appetite, mucositis and/or oral aphthae, sweating). Our study demonstrated the lowest risk of hematological toxicities associated with PEG-IFN-α-2a (15,19,20). A total of 3 patients (1 PV, 2 ET) developed autoimmune toxicities. All cases were reported as autoimmune thyroiditis. The median duration of treatment in this group of patients was 24 months. In a long-term follow-up clinical trial (almost 7 years) of PEG-IFN-α-2a, adverse effects appeared to become less frequent over time. 10-17% of patients developed new grade 3/4 toxicities following 24 months of treatment (15). For most of our patients, the incidence of adverse events decreased over time.

In the CYTO-PV study, there was a four-fold reduction in the incidence of major thrombosis in the group with a HCT of less than 45% than in the group with a target HCT of 45% to 50% (21). However, this is difficult to achieve in a short period of time. PROUD/CONTI-PV trials confirms an improved hematologic response with treatment extension in the group receiving ropeginterferon alfa-2b (22). Likewise, in a small chort study, HCT control with ropeginterferon appeared to be unsatisfactory (23). We showed here that the HCT tends to fall slowly, with 69% of patients were in the 45.5-48% HCT range. On another point, PEG-IFN-α-2a reduced the need for phlebotomies (in all but one) and >50% of PV patients became phlebotomy-free. Impressively, the number of phlebotomies required in one PV patient was reduced from 48 to 4 per year with therapy. This also contributed to the reduction in the number of imperative hospital admissions during the COVID-19 pandemic.

In recent trials, the association between leukocytosis and thrombosis has been more questionable (24). On the contrary, the median white blood cell count decreased from 12.4×10^9/L (IQR, 9-14.3) at baseline to 5.7×10^9/ L (IQR, 4.4-8.5) at the end of the study, coupled with a rapid platelet normalisation

[median value was 614×10^9/L (IQR, 280-938) at baseline and 275×10^9/L (IQR, 199-441) at endpoint]. Our experience suggests that PEG-IFN-α-2a may provide superior efficacy in ET patients. Similarly, data from the MPD-RC-111 study manifested that CHR was higher in patients with ET (43%) than in those with PV (22%) (16). This can be explained by the anti-proliferative effect of interferons and the half-life of hematopoietic stem cells (platelets<leukocytes<red blood cells).

Study Limitations

This study has limitations due to its retrospective nature. In addition, moleculer and histological remission status was not quantified in the majority of patients. In some subjects, the JAK2V617F mutation status was analysed as positive regardless of allele burden.

Recent data support that a high JAK2V617F allele burden increases the risk of venous thrombosis (25). However, we found no significant difference in the occurrence of thrombosis among patients who had or had not a JAK2 mutation status prior to PEG-IFN-α-2a treatment (1 PV, 7 ET; 4 JAK2-positive, 4 JAK2-negative). Only one venous thrombosis was recorded in a JAK2-positive case during treatment. We did not observe a link between the baseline JAK2V617F mutation status and achieving a CHR. Some reports have indicated a connection between a reduction in the frequency of the JAK2V617F variant allele and clinical response, with a particular emphasis on its significance in patients with PV (6,15,16).

Published studies have confirmed that bone marrow responses are achieved after a median treatment duration of 48 months (26). The median time to follow-up was 28 months (range, 13-47) in a limited number of patients with bone marrow non-response in our report. One of these patients also completely lost her best HR (CHR) and underwent an allogeneic stem cell transplantation for ET with myelofibrosis transformation. However, although the fibrosis grade increased by one level in a patient with PV, there is little doubt that not repeating bone marrow biopsy for confirmation, as suggested by Masarova et al. (26).

Conclusion

In conclusion, PEG-IFN-α-2a has beneficial effects in our real-world MPN patients, consistent with previous reports. Further prospective, long-term monitoring studies are required to evaluate the effects of PEG-IFN-α-2a on the dynamics and significance of clinical-hematological, molecular and morphological responses. In patients with a poor response to PEG-IFN as a single agent, PEG-IFN-based combination therapy may improve response. The acquisition of clonal genetic mutation analysis is invaluable to the efficacy of PEG-IFN and warrants investigation.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (date: 10.12.2021, approval no.: İ10-663-21).

Informed Consent: Since this was a retrospective study, patient consent was not obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practice: D.K., G.C.S., S.C.B., S.K.T., P.T., Ö.A., M.Ö., Concept: D.K., M.Ö., Design: D.K., M.Ö., Data Collection or Processing: D.K., Analysis or Interpretation: D.K., Literature Search: D.K., M.Ö., Writing: D.K.

Conflict of Interest: There is no potential conflict of interest to declare.

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