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EFFECTIVENESS OF ROPEGINTERFERON ALFA-2B IN HIGH-RISK PATIENTS WITH PHILADELPHIA CHROMOSOME NEGATIVE MYELOPROLIFERATIVE NEOPLASMS– EVALUATION OF CLINICOHAEMATOLOGIC RESPONSE, AND SAFETY PROFILE: SINGLE CENTRE EXPERIENCE

Marija Popova-Labachevska, Milche Cvetanoski, Nevenka Ridova, Sanja Trajkova, Simona Stojanovska-Jakimovska, Tara Mojsovska, Zlate Stojanoski, Aleksandra Pivkova-Veljanovska, Irina Panovska-Stavridis

University clinic of hematology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, RN Macedonia

Corresponding author: Marija Popova-Labachevska MD, PhD candidate, University Clinic of Hematology-Skopje, Republic of North Macedonia, Majka Tereza 17, 1000 Skopje, RN Macedonia, tel/fax:+38923111749, e-mail: marijapopova85@yahoo.com; Irina Panovska-Stavridis, MD, PhD, University Clinic of Hematology-Skopje, Republic of North Macedonia, Majka Tereza 17, 1000 Skopje, RN Macedonia, tel/fax:+389 2 3111749, e-mail: dr_irina@yahoo.com

ABSTRACT

Background: Treatment of Philadelphia chromosome negative myeloproliferative neoplasms (Ph – MPNs) requires individualized approach depending on multiple factors. Novel pegylated Interferon (IFN) formulations have become an attractive therapeutic option in young Ph- MPN patients associated with better patient compliance.

Methods: In this retrospective observational study a total of 16 high-risk Ph- MPN patients treated off-label with ropeginterferon alfa-2b given twice monthly, were included. Median follow-up was 24 months. High-risk patients were defined using the IPSET score. Response to treatment was evaluated using ELN, IWG-MET EUMNET standardized criteria and occurrence of side effects was documented.

Results: 11 patients were female (68.8%) and 5 male (31.2%); average age at diagnosis was 36 years (17-51); 12 patients (75%) had ET, one (6.2%) PV and three (18.8%) hypercellular phase of PMF. JAK2V617F mutation was detected in 10 patients (62.5%), CALR in three (18.8%), and three (18.7%) were triple-negative cases. In 7 patients (43.7%), ropeginterferon alfa-2b was used in first-line, and 9 (56.3%) were previously treated with HU and/or standard IFN. Among initially ropeginterferon alfa-2b treated patients, complete haematological response was observed in 4/7 (57.1%), partial in 2/7 (28.6%) and suboptimal in one (14.3%). Complete haematological response was observed in 8/9 (88.9%) among previously treated patients. Average time to blood count normalization was 8 weeks, at a dose ranging between 100mcg and 300mcg. Side effects were observed in one patient (6.2%).

Conclusion: Our experience is in support of previous studies regarding ropeginterferon alfa-2b efficacy and safety profile in the treatment of young patients with Ph- MPNs.

Keywords:Essential Thrombocythemia, Polycythemia Vera, Primary Myelofibrosis, myeloproliferative neoplasms, ropeginterferon alfa-2b

INTRODUCTION

Philadelphia chromosome negative (Ph-) myeloproliferative neoplasms (MPNs) comprise a group of heterogeneous clonal diseases of myeloid origin characterized by uncontrolled production of terminally differentiated myeloid cells. Hallmark of the disease is the presence of mutually exclusive Janus kinase (JAK), calreticulin (CALR) and myeloproliferative leukemia virus oncogene (MPL) mutations, referred as "phenotypic driver" mutations because of their role in promoting myeloproliferative phenotype [1].

Classical Ph - MPNs include three major subtypes: Essential Thrombocythemia (ET), Polycythemia Vera (PV) and Primary Myelofibrosis (PMF). Each of them is defined by their own unique genotypic abnormalities, symptom profile, complications and prognosis [2]. Although clinically they share similar constellation of symptoms including constitutional symptoms and propensity towards thrombosis or bleeding, the rates of disease transformation into acute leukemia or secondary myelofibrosis (for ET and PV) differ among each other. While best prognosis is seen in the ET setting where the median survival is similar to age-matched controls, myelofibrosis (MF) either primary or secondary from ET or PV, is the most debilitating MPN subtype with worst prognosis [3].

For more than three decades Interferon (IFN) has been acknowledged as an effective treatment option in patients with Ph- MPNs. Unlike other available drugs like hydroxyurea (HU), and anagrelide (ANA), Interferon was shown to induce not only clinico-haematological but also molecular responses in a significant proportion of MPN patients, thus modifying the course of the disease [4]. This unique IFN feature is based on its ability to suppress clonal hematopoiesis in this setting of patients. However, because of HU capability to normalize blood counts, with subsequent reduction of the risk of thrombohemorrhagic events, it is still considered as conventional and reasonable therapeutic option used widely, especially in older patients [5]. Still, real world experience has shown that long-term exposure to HU is associated with multiple side effects leading to drug cessation in half of the MPN patients [6]. On the other hand, ANA, although frequently used in young patients or alternatively to HU, has been associated with higher rates of progression to bone marrow fibrosis so its potential impact remains controversial [7, 8]. Both, HU and ANA have an established potential teratogenicity and infertility, and are not recommended in pregnancy, so treatment of young Ph- MPN patients with reproductive potential is often challenging [6, 7, 8].

Recent studies have turned the spotlight on the novel pegylated IFN formulations because of their association with fewer treatment related adverse events, and less frequent administration leading to better patient compliance, making them superior to classical IFNs [9]. In addition, given that many systematic reviews have shown no increase in adverse pregnancy outcomes using IFN, this therapeutic modality is the treatment of choice in young MPN patients [9, 10].

Ropeginterferon alfa-2b is a third generation, site-specific, monopegylated, stable IFN-alfa analog that has emerged as an important therapeutic tool, currently approved only for treatment of patients with Polycythaemia Vera (PV) [11]. However, many studies are evaluating the efficiency of the drug in patients with ET and PMF with final intention to expand its usage in other MPNs as well [12]. In order to clarify these observations, we present our experience with off-label use of ropeginterferon alpha-2b in 16 young patients with MPN, diagnosed and treated at the University Clinic of Haematology in Skopje, Republic of North Macedonia.

MATERIAL AND METHODS

This is a retrospective observational study in which 16 Ph- MPNs patients treated with ropeginterferon alfa-2b were included. The starting dose of the drug was 100mcg with allowed dose escalation of 50mcg every two weeks if needed. Median follow-up of the patients was 24 months. Diagnosis of Ph- MPN was made according to WHO 2016 criteria. For diagnosis confirmation purpose, bone marrow biopsy before treatment initiation was performed in all patients. The presence of JAKV617F, CALR and MPL mutations from peripheral blood DNA was performed with multiplex fluorescent allele-specific polymerase chain reaction (PCR) technique using custom designed primers. Patients were classified as high-risk according to the revised IPSET (Internation-

al Prognostic Score for ET) score. Response to treatment was evaluated using ELN, IWG-MET EUMNET standardized criteria sets and occurrence of side effects was recorded. The study was approved by the local Institutional Review Board at the clinic and all patients provided written informed consent.

RESULTS

In our cohort 11 were female (68.8%) and 5 were male (31.2%) patients, with average age at diagnosis of 36 years (17-51). In terms of diagnosis, 12 patients (75%) had ET, one (6.2%) had PV and three patients (18.8%) had hypercellular phase of PMF according to the European consensus on grading bone marrow fibrosis and assessment of cellularity. According to the mutational status, JAK2V617F mutation was detected in 10 patients (62.5%), CALR mutation in three (18.8%), and three patients were designated as triple-negative cases (18.7%). Th average Hemoglobin (Hb) count before the initiation of the treatment in all of the patients was 136 (101-159) g/L, white blood cell count (WBC) was 9.8 (5-23) x109/L and platelet (Plt) count was 996 (161-2699) x109/L. In 7 high-risk patients (43.7%), ropeginterferon alfa-2b was used as first-line treatment, and the remaining 9 patients (56.3%) were previously treated with HU and/or standard interferon alfa-2a, of which two entered the study with already attained haematological response. Splenomegaly assessed by physical examination and ultrasound was present in four patients (25%), while three patients underwent splenectomy because of splenic vein thrombosis which was MPN associated. Evaluation of the clinico-haematological response was performed every two weeks along with the drug administration. Among the patients in which ropeginterferon alfa-2b was used as first-line treatment, complete haematological response was observed in 4/7 (57.1%), 2/7 (28.6%) patients achieved partial haematological response with ≥50% reduction from the baseline blood values and one (14.3%) patient exhibited suboptimal therapeutic response with ≤25% reduction of the baseline blood values. A complete haematological re-

Table 1. *Baseline characteristics of patients that underwent treatment with ropeginterfeon alfa-2b*

Patients initials	Age	Sex	Diagnosis	Year of diagnosis	Mutation	Spleen (cm)	Dosage of ropeginterferon alfa-2b	Initial Hb g/L	Initial WBC 10/9 L	Initial Plt 10/9 L	Control Hb g/L	Control WBC 10/9 L	Control Plt 10/9 L
EJ	29	f	ET	2016	JAK2+	11	300mg	133	6.3	1138	141	5.4	435
ST	34	f	ET	2011	JAK2+	17	100mg	126	8	213	133	11	423
MS	17	f	PRV	2021	triple neg	splenectomy	250mg	136	8	998	125	14	612
MS	43	f	ET	2016	JAK2+	15	100mg	149	8	1035	125	10	355
AA	51	m	ET	2016	triple neg	11	150mg	139	5.6	161	157	7.5	241
AG	30	m	ET	2021	CALR+	12	150mg	159	10	1160	150	6	369
EA	37	f	ET	2015	JAK2+	16	100mg	146	10	820	145	6	285
KK	34	f	PMF	2017	triple neg	11	150mg	109	7	611	113	6	846
ISM	31	f	PMF	2016	JAK2+	12	250mg	151	15	895	143	7	375
JK	39	f	PMF	2021	JAK2+	14	150mg	155	15	1000	147	9	517
EA	20	m	ET	2022	CALR+	11	100mg	126	8.4	1270	115	4	330
FR	25	f	ET	2019	CALR+	12	150mg	131	9	1263	136	4	512
SM	19	f	ET	2022	JAK2+	splenectomy	150mg	132	6.5	632	126	6.9	577
BI	23	m	ET	2022	JAK2+	11	250mg	155	11	1213	135	8	300
ZK	34	m	ET	2021	JAK2+	splenectomy	300mg	101	23	2699	131	13	727
MJ	25	f	ET	2016	JAK2+	11	300mg	140	7	835	138	4	290

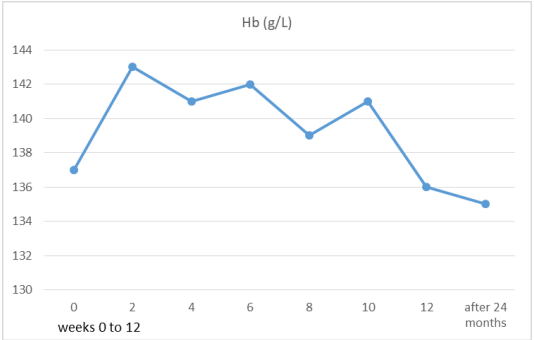

Figure 1. Mean hemoglobin (Hb) values dynamics from treatment start over the first 12 weeks and after 24 months follow-up in those patients in which ropeginterferon alfa-2b was used as first line treatment.

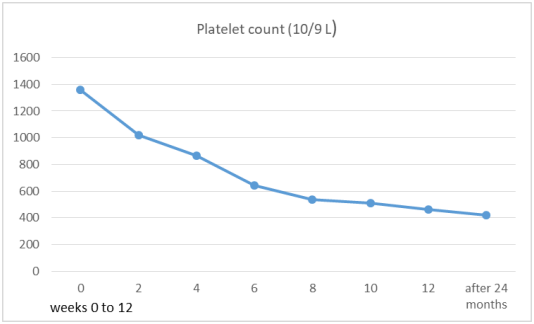

Figure 2. *Mean platelet (Plt) values dynamics from treatment start over the first 12 weeks and after 24 months follow-up in those patients in which ropeginterferon alfa-2b was used as first line treatment.*

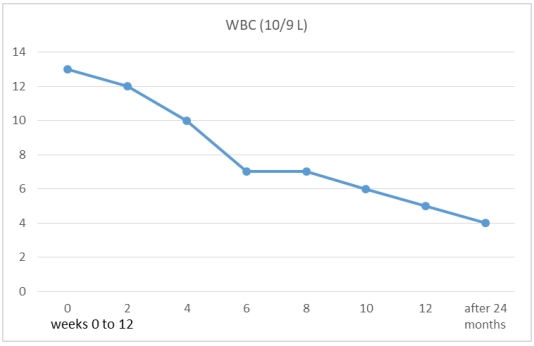

Figure 3. *White Blood Cell (WBC) values dynamics from treatment start over the first 12 weeks and after 24 months follow-up in those patients in which ropeginterferon alfa-2b was used as first line treatment.*

sponse was observed in 8/9 (88.9%) among the previously treated patients, and a partial response in one (11.1%) patient. The average time to blood count normalization was at 8 weeks, at a dose ranging between 100mcg and 300mcg without dose limiting toxicities. In terms of side effects, only mild flu-like symptoms were observed in one patient (6.2%) without need of drug discontinuation or dose modification. During the follow-up period, none of the patients experienced disease progression.

DISCUSSION

In ideal circumstances, the treatment of ET patients should provide adequate control of platelet count, amelioration of ET-related symptom burden, decrease of thrombotic and haemorrhagic risk and prevention of disease progression to post-ET myelofibrosis at the same time [13]. Low-dose aspirin with hydroxyurea (HU) is long established first-line therapy for high-risk ET patients. However, studies have shown that approximately 25% of ET patients become HU resistant or intolerant over time which makes them to be at an increased risk of thrombosis and disease transformation [5]. Long-term exposure to HU has been associated with secondary cancers including skin cancers [6] .There are data that currently approved second-line treatment option anagrelide (ANA) is associated with higher incidence of myelofibrosis transformation which underlines the importance of periodic monitoring for the presence of bone marrow fibrosis and careful use in young patient population [7, 8, 14]. Both, HU and anagrelide as previously mentioned have shown teratogenicity and effects on fertility, so when making treatment decisions in young patients with a perspective to be lifelong exposed to HU or anagrelide, it is crucial to consider both efficacy and long-term side effects [7, 8]. Since studies have already proven the disease modifying properties of IFN by its ability to eliminate malignant clones harboring JAK2V617F or CALR mutations in MPN patients, great efforts to produce more tolerable IFN formulations have been made [4]. Our experience is encouraging and in parallel with previously reported results regarding ropeginterferon alfa-2b efficiency and safety profile with complete haematological response observed in 57.1% of the patients in which ropeginterferon was used as first-line. Additionally, complete haematological response was achieved in 88.9% of the patients previously treated with other drugs. Adverse events were noted in only one patient experi-

encing mild flu-like symptoms (6.2%). Since currently ropeginterferon alfa-2b is approved only for PV patients, results from its off-label use in high-risk young ET patients and ET patients who are HU intolerant or resistant are promising, further imposing the need to broaden its use and finally fill the paucity of guiding treatment in ET and PMF [15].

CONCLUSION

In summary, our results suggest that ropeginterferon alfa-2b is safe in the administered dose range and exhibits profound efficacy, regarding normalization of blood parameters and subsequent vascular event reduction. Since this novel IFN formulation allows a more convenient treatment schedule accompanied by low toxicity while obtaining high haematologic and molecular response rates, we support the necessity to expand its use in the treatment of young high-risk patients with ET and PMF.

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Резиме

ЕФИКАСНОСТ НА ROPEGINTERFERON ALFA-2B КАЈ ПАЦИЕНТИ СО ФИЛАДЕЛФИЈА ХРОМОЗОМ НЕГАТИВНИ МИЕЛОПРОЛИФЕРАТИВНИ НЕОПЛАЗМИ СО ВИСОК-РИЗИК – ЕВАЛУАЦИЈА НА КЛИНИЧКО-ХЕМАТОЛОШКИОТ ОДГОВОР И БЕЗБЕДНОСЕН ПРОФИЛ: НАШИ ИСКУСТВА

Марија Попова-Лабачевска, Милче Цветаноски, Невенка Ридова, Сања Трајкова, Симона Стојановска-Јакимовска, Тара Мојсовска, Злате Стојаноски, Александра Пивкова-Велјановска, Ирина Пановска-Ставридис

Универзитетска клиника за хематологија, Универзитет „Св. Кирил и Методиј“, Медицински факултет, Скопје, РС Македонија

Вовед: Третманот на пациентите со филаделфија хромозом негативни миелопролиферативни неоплазми (МПН) со висок ризик: есенцијална тромбоцитемија (ЕТ), вистинска полицитемија (ВП) и примарна миелофиброза (ПМФ), претставува предизвик. Администрацијата на ropeginterferon alfa-2b се спроведува на подолг временски интервал и е асоциран со помал процент несакани ефекти, но во моментот официјална дозвола за употреба има само за третман на ВП.

Материјали и методи: Во оваа ретроспективна, опсервациска студија беа вклучени вкупно 16 пациенти со МПН со висок ризик и беа поставени на терапија со ropeginterferon alfa-2b двапати месечно, надвор од одобреното индикациско подрачје. Просечното време на следење на пациентите изнесуваше 24 месеци. Високоризичните МПН-пациенти беа дефинирани според ризик-скорот IPSET. Одговорот беше евалуиран според ELN, IWG-MET EUMNET стандардизирани критериуми и пациентите беа следени за евенутална појава на несакани настани.

Резултати: Од вкупно 16 пациенти, 11 (68,8 %) беа жени, а 5 (31,2 %) беа мажи, со просечна возраст од 36 (17–51); 12 (75 %) пациенти имаа ЕТ, еден (6,2 %) ВП, а три (18,8 %) пациенти хиперцелуларна фаза на ПМФ. JAK2V617F мутацијата беше детектирана кај 10 (62,5 %) пациенти, CALR кај три (18,8 %), а три (18,7 %) пациенти беа негативни за сите три водечки мутации. Кај 7 (43,7 %) пациенти ropeginterferon alfa-2b беше употребен како прволиниска терапија, а 9 (56,3 %) беа претходно лекувани со други тераписки модалитети. Меѓу оние пациенти што беа лекувани со ropeginterferon alfa-2b во прва линија, комплетен хематолошки одговор беше постигнат кај 4/7 (57,1 %), парцијален кај 2/7 (28,6 %) а субоптимален одговор беше забележан кај еден (14,3 %) пациент. Комплетен хематолошки одговор беше постигнат кај 8/9 (88,9 %) пациенти претходно лекувани со друга терапија. Просечното време за нормализација на крвната слика беше 8 недели од почнување на терапијата, во дози од лекот меѓу 100 mcg и 300 mcg. Несакани ефекти беа нотирани кај само еден пациент (6,2 %).

Заклучок: Нашето искуство покажа дека, покрај клинико-хематолошкиот одговор во поглед на нормализацијата на хематолошките параметри, ropeginterfeon alfa-2b има и адекватен безбеднос профил, отварајќи ја можноста за проширување на неговата употреба не само кај пациентите со ВП туку и кај оние со ЕТ и ПМФ.

Клучни зборови:есенцијална тромбоцитемија, вистинска полицитемија, примарна миелофиброза, миелопролиферативни неоплазми, ropeginterferon alfa-2b