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Change in Polycythemia Vera Treatment: Ropeginterferon Alfa-2b in Light of Current Trials

Polisitemia Vera Tedavisinde Değişim: Mevcut Çalışmalar Işığında Ropeginterferon Alfa-2b

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Abstract

Ropeginterferon alfa-2b (RopegIFN) enables effective cytoreduction in polycythemia vera (PV). Recent analyses suggest that long-term RopegIFN therapy fulfills treatment goals important to patients with PV including good quality of life, the slowing of disease progression, and long event-free survival. Data support the use of RopegIFN in both early PV therapy and second-line and beyond.

Keywords: PH-negative chronic myeloproliferative neoplasm, Chronic myeloproliferative neoplasms, Neoplasia, Hematopoietic stem and progenitor cells, Hematopoiesis, Pharmacotherapeutics, Neoplasia, Oncogenes

Öz

Ropeginterferon alfa-2b (RopegIFN), polisitemia vera (PV) hastalığında etkili bir sitoredüksiyon sağlar. Son analizler, uzun vadeli RopegIFN tedavisinin, PV'li hastaları için önemli olan tedavi hedeflerini karşıladığını göstermektedir. Bu hedefler arasında iyi bir yaşam kalitesi, hastalığın ilerlemesinin yavaşlatılması ve uzun süreli olaydan bağımsız sağkalım bulunmaktadır. Veriler, RopegIFN'nin erken dönem PV tedavisi ile ikinci basamak tedavi ve sonrasında kullanımını desteklemektedir.

Anahtar Sözcükler: PH-negatif kronik myeloproliferatif neoplazm, Kronik myeloproliferatif neoplaziler, Neoplazi, Hematopoetik kök ve progenitör hücreler, Hematopoiesis, Farmakoterapötikler, Neoplazi, Onkogen

Introduction

Therapy for polycythemia vera (PV) aims at control of clinical symptoms and lowering of the risk of thromboembolism, bleeding, and disease progression to myelofibrosis and acute leukemia. In early disease and in patients with low disease burden, therapy involves phlebotomy and low-dose acetylsalicylic acid [1]. Additional cytoreductive therapy is required for high-risk patients (aged >60 years or with previous thrombotic events) and for low-risk patients with progression of myeloproliferation, increasing thromboembolic/bleeding risk, uncontrollable symptoms, or poor tolerance to phlebotomy.

Hydroxyurea (HU) is available for first-line cytoreductive therapy in PV. However, response to HU may be limited by the occurrence of resistance and intolerance and may thus fail to prevent disease progression. Furthermore, this chemotherapeutic agent is suspected to promote leukemia and is associated with secondary skin malignancies and genotoxicity.

Treatment guidelines for PV recommend the use of interferon alpha (IFN-α) as an alternative to HU for first-line cytoreductive therapy [1]. Advantages of IFN-α over HU include the lack of genotoxicity, carcinogenicity, and leukemogenic potential. Pegylated IFN-α is preferred, since it has less side effects compared to conventional IFN-α and the rates of discontinuation due to toxicity are decreased. Interferons are especially used for younger patients, or when HU-associated toxicities/intolerances are an issue. Importantly, interferons are the only compounds inducing selective decrease of malignant stem cells; therefore, they are disease-modifying [2].

The only IFN-α licensed for PV in the EU is ropeginterferon alfa-2b (RopegIFN), a novel pegylated IFN with an extended half-life [3]. In the following, I summarize the therapeutic profile of RopegIFN in PV emerging from recent clinical trials.

Higher Response with RopegIFN

In the pivotal phase 3 study PROUD-PV, patients diagnosed with high-risk PV who were cytoreduction-naive or HU-pretreated

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were randomized to RopegIFN or HU for 1 year [4]. In the extension study CONTINUATION-PV (n=169), patients in the HU arm could switch to the best available therapy (BAT); final efficacy analysis was conducted once all patients completed 6 years of treatment, with a maximum treatment duration of 7.3 years [5].

The results agreed with those of previous interim analyses [4,6], demonstrating higher rates of complete hematologic response (CHR) among RopegIFN-treated patients compared to the control group (54.6% vs. 34.9%, p=0.02), and of molecular response (MR; 66.0% vs. 19.4%, p<0.0001).

Achieving Patient-centered Treatment Goals with RopegIFN

To improve quality of life, PV therapy should ameliorate symptoms while reducing phlebotomies to avoid adverse effects associated with iron deficiency. Symptoms were reported in 15.7% of patients in the RopegIFN arm and 20.7% in the control arm during the 6th year of treatment [5]. Among the ten most relevant PV-related symptoms, six occurred at a lower frequency during the 6th year of treatment with RopegIFN compared to the 1st year (after week 4), including pronounced reduction of fatigue and itching. In the 6th year of treatment, no phlebotomies were required to maintain hematocrit below 45% in 81.4% of patients receiving RopegIFN compared to 60.0% in the control arm (p=0.005) [5].

From the patients' perspective, slowing disease progression is of highest priority [7]. The risk of progression of PV to secondary myelofibrosis may be lowered by reducing the *JAK2* V617F allele burden [8]. During RopegIFN treatment, the allele burden steadily declined (Figure 1) [6]; after 6 years, it decreased to below 1% in 20.7% of patients versus only 1.4% of patients in the control arm (p=0.0001) [5].

A further important goal is the prevention of thromboembolic complications. During PROUD-PV/CONTINUATION-PV, risk events (thromboembolic episodes, disease progression, and death) were monitored. The probability of event-free survival was significantly higher among patients treated with RopegIFN compared to the control arm (Figure 2).

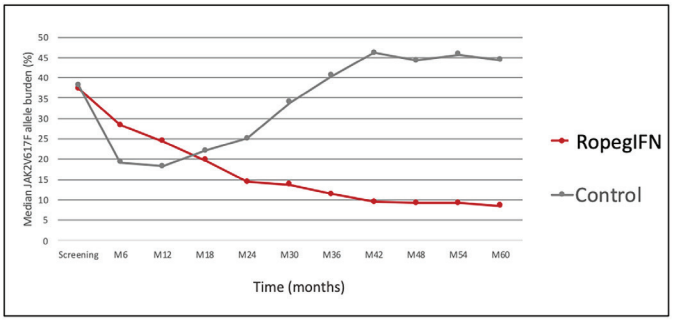

Figure 1. Time course of *JAK2* V617F allele burden [6].
RopegIFN: Ropeginterferon alfa-2b.

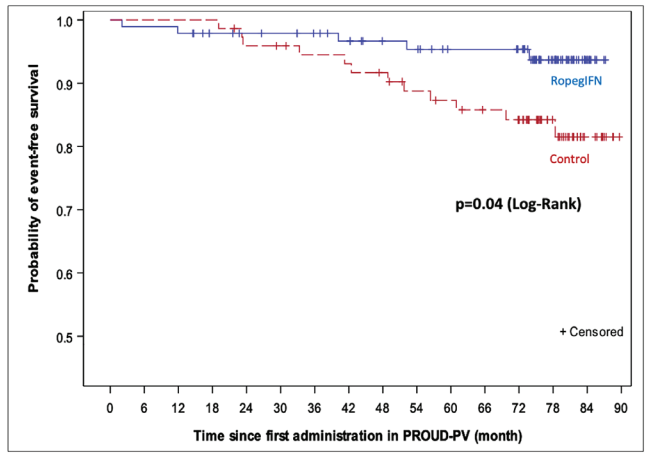

Figure 2. Event-free survival during the PROUD-PV/CONTINUATION-PV study [5].
RopegIFN: Ropeginterferon alfa-2b.

In summary, with long-term RopegIFN therapy treatment, goals important to PV patients are achievable: good quality of life as indicated by a low symptom burden and low phlebotomy requirements, potential to influence disease progression, and a higher probability of event-free survival compared to BAT.

RopegIFN as Second-line Therapy

In PROUD-PV/CONTINUATION-PV, high rates of CHR and MR were sustained at 5 years in both HU-naive and HU-pretreated patients in the RopegIFN arm [9]. Although early initiation of RopegIFN is thought to have the greatest disease-modifying benefit in patients with PV, these data suggest that RopegIFN is also a suitable treatment option in patients switching from therapy with HU.

In the Daliah trial including patients with myeloproliferative neoplasms, pegylated IFN-α-2a and -2b were associated with a discontinuation rate due to treatment-related toxicity of 34% at 24 months [10]. In contrast, the discontinuation rate of RopegIFN in PROUD-PV/CONTINUATION-PV due to drug-related events was 10% over at least 5 years [9]. Besides the prolonged half-life, this appears as a clear advantage of RopegIFN over other interferons.

PV Patient Cases: IFN-α Toxicity/Intolerance

- A PV patient treated with seven weekly 90-µg doses of pegylated IFN-α-2a showed pronounced elevation of liver enzymes. After stopping therapy, values normalized, but went up again upon restarting. Therapy was then switched to RopegIFN (125 µg every 4 weeks), which did not induce any liver toxicity.
- Neuropsychiatric side effects are known to be associated with IFN. A PV patient receiving pegylated IFN-α-2a (135 µg every 2 weeks) had to stop therapy after 1 year because of panic attacks. This side effect did not reoccur under subsequent RopegIFN therapy (concomitant with low-dose ruxolitinib).

In summary, RopegIFN may also be considered as second- or third-line therapy in patients pretreated with different pegylated interferons, avoiding the limiting side effects of the latter [11].

As an alternative to IFN-α, ruxolitinib is also an appropriate second-line drug for PV patients who are intolerant or have inadequate response to HU. In the absence of a direct comparison of these two agents, the choice should be based on the patient's age, as suggested by current guidelines [1]. Recombinant interferon-α-2b (rINF-α) should be preferred for young patients in need of long-term treatment.

Conclusion: Transforming PV Therapy

RopegIFN has changed the contemporary management of PV. It provides higher hematological and molecular response than HU and meets the expectations of patients regarding disease control. Furthermore, RopegIFN is better tolerated than other types of IFN-α and is more convenient due to less frequent dosing. In addition to treating high-risk PV, evidence from a randomized controlled study demonstrated the superiority of RopegIFN compared to phlebotomy alone in maintaining hematocrit within the target range [12,13]. The accumulating evidence supporting the use of RopegIFN in defined subgroups of low-risk patients has led to a new treatment algorithm in PV [14].

Ethics

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