Complete hematological and major molecular response through treatment with ultra-low dose Interferon alpha 2 in polycythemia vera: a case report

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Abstract

Early treatment of polycythemia vera with ultra-low-dose interferon-α 2a is well tolerated and results in complete hematologic and major molecular remission and a strong reduction of all symptoms, especially pruritus and fatigue.

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Key Clinical Message

Early intervention with ultra-low-dose interferon-α 2a should be considered as an alternative to watch and wait therapy with aspirin and phlebotomies, especially in young polycythemia vera patients.

Abstract

Early treatment of polycythemia vera with ultra-low-dose interferon-α2 is well tolerated and results in complete hematologic and major molecular remission and a strong reduction of all symptoms, especially pruritus and fatigue.

KEYWORDS

Polycythemia vera, interferon, ultra-low dose

Introduction

Polycythemia vera (PV) belongs to a group of Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET) and primary myelofibrosis (PMF), the latter including prefibrotic PMF [1]. MPNs are myeloid malignancies, which are characterized by stem cell derived clonal myeloproliferation. A constitutive activation of the JAK2/STAT-signaling pathway plays an important role in the pathogenesis of MPNs. In at least 97% of all PV-patients, this activation is caused by a somatic gain-of-function mutation of the Janus kinase 2 gene (JAK2)[1]. PV is a rare disease and can occur at any age, but the median age at diagnosis is 59 years. It is generally considered benign and the overall 15-years survival was 65% with a median survival exceeding 20 years [2].

Case Presentation

We report on a 50-year-old male patient with suspected PV presented himself in October 2017 in our hematological clinic. He reported on first episodes of generalized aquagenic pruritus occurred in November 2016, and two small vein thromboses in the posterior tibial and femoropopliteal veins in January and July 2017, respectively, both after long-distance flights. In connection with the second venous thrombosis other elevated blood values appeared (figure 1). The patient was initially treated with the factor Xa-inhibitor rivaroxaban (Xarelto®, 20 mg OD) to prevent recurrent venous thrombosis and took no other medication, had a good health status, normal weight (BMI 22 kg/m^2) and was non-smoker. There were no other significant previous illnesses. A transabdominal ultrasound revealed a normal spleen size of 12.2 cm and no abnormalities in the kidneys, liver, gallbladder, pancreas or abdominal aorta.

Due to increased hematocrit and thrombocytosis, genetic testing for PV was performed confirming a *JAK2V617F* -mutation. No other somatic mutations in 40 key DNA genes to cover all the major myeloid disorders were found with the targeted NGS assay (Fisher Scientific AG, Reinach, Switzerland). A bone marrow biopsy showed megakaryocyte proliferation and was slightly hyper-cellular with partially transformed erythropoiesis. There were no signs of a progenitor or fiber proliferation. Serum erythropoietin (EPO)-level (5.2 U/L) and serum ferritin (31 µg/L) were both in the low-normal range, as typically for PV.

As the patient performed annual medical check-ups since 2013, the development of his blood values could be re-examined. Between July 2013 and September 2017, erythrocyte, thrombocyte and leukocyte counts increased steadily with all values still in the normal range. Hematocrit (Hct) rose from 0.44 in 2013 to 0.54 in September 2017. During the same period hemoglobin (Hb) increased from 159 g/L to >180 g/L. In August 2017, platelets (350 G/L) were for the first time above the normal range of 150-300 G/L. Retrospectively, a slow development of a polycythemia vera was seen, which was still in its early stage at the time of diagnosis in October 2017, with only moderately increased hematopoiesis (figure 1).

Since the patient had already two events of venous thrombosis, he was classified as high-risk patient with the consequence of an initial cytoreductive treatment. However, based on the diagnosis of PV at an early stage, his age and his overall health status, the treatment was started with phlebotomies. Seven phlebotomies (450 mL each) were required to reach the target Hct of <0.45. In February 2018, the patient was switched from rivaroxaban to low-dose aspirin (75 mg morning / 50 mg evening).

To keep the target Hct of <0.45, further phlebotomies every 4 weeks were required. As the patient had already low iron levels (ferritin 31 µg/L) prior to the onset of therapeutic phlebotomy, a severe iron deficiency anemia with ferritin values of <10 µg/L and characteristic microcytes with mean corpuscular volume (MCV) of <

80 fL developed rapidly (figure 1). The increasing anemia led to an elevated symptom burden with more severe pruritus, restless-leg-syndrome, fatigue and shortness of breath.

In February 2018, a first quantitative measurement of the JAK2V617F-allele burden (MutaQuant Kit, Quiagen) was performed showing an allele burden of 52% that remained almost stable until July 2018.

Phlebotomies were suspended in April 2018, but had to be restarted in August 2018 due to rebounding Hct-values. Interestingly, parallel to the interruption of phlebotomies, the JAK2V617F-allele burden increased steadily to 84% and remained at that plateau (figure 1).

Due to disease progression with increasing leukocytosis, erythrocytosis and thrombocytosis as well as increasing symptom and JAK2V617F-allele burden, we decided to switch the therapy to pegylated interferon-α2 (IFN-α-2a; Pegasys®), in January 2019. Since, an initial low dose of 45 µg/week of IFN-α-2a was proposed to improve initial tolerability[3], an ultra-low starting dose of 30 µg/week was chosen as starting dose. However, after only one month of treatment with IFN-α-2a, white blood cells (WBC) were back in the normal range (from 14.3 g/L to 7.3 g/L) and platelets were markedly reduced from 556 g/L to 473 g/L. We therefore decided, not to escalate the dose further and to keep the dose at 30 µg/week. Parallel to the ultra-low dose IFN-α-2a treatment a cautious oral iron (i.e., iron-2-gluconate) substitution with 14 mg /day was initiated. In the course of further therapy, all blood values normalized. After normalization of the platelet count in May 2019, the low-dose aspirin was reduced from 125 mg / day to 1 x 100 mg / day.

As the low mean corpuscular volume (MCV)-value (66 fL) normalized faster compared to the red blood cells (RBC), and as the leucocytes were back in the normal range (7.0 g/L) it was decided to accept Hct-values of >0.45 and to dispense further phlebotomies. At the same time, reduced reticulocytes indicated a reduced hematopoiesis. Eleven months after therapy start with IFN-α-2a, a complete hematological remission was reached (figure 1).

Parallel to the normalization of the blood count, all symptoms, especially aquagenic pruritus and restless-leg-symptom disappeared. With the normalization of the iron status, the patient felt much better. In November 2019, the ferritin value returned back to normal range at 144 µg/L and the iron substitution was suspended. In April 2021, the JAK2V617F-allele burden decreased to 10% (figure 1).

The treatment with ultra-low dose IFN-α-2a was well tolerated, with only very mild fatigue at the day after subcutaneous injection and a redness at the injection site.

Discussion

The recommended first-line treatment for low-risk PV patients consists of phlebotomy and low-dose aspirin; the latter only if not contraindicated [4]. In newly diagnosed PV patients, phlebotomy remains the cornerstone of therapy, with the goal to reduce elevated Hct to <0.45 and to expand the plasma volume[5]. Besides removing excess red blood cells, a decreased hemoglobin synthesis and hence decreased MCV, plays an important role in the decreased Hct after phlebotomy.

However, since Hct is calculated as Hct = MCV * RBC, it is evident that a target Hct of <0.45 can result from very different combinations of MCV and RBC and thus might lead to different risk of thrombosis. On the other hand, combinations of MCV and RBC well within their normal ranges may cause Hct to rise above the upper limit of the normal range. An identical Hct of 0.45 can result from an RBC of 4.7 and MCV of 95 or from an RBC of 5.6 and MCV of 80. However, it is obvious that the viscosity and clotting risk is likely to differ.

Investigations of Edelman and colleagues on the role of integrins on the surface of leukocytes for the thrombus formation in JAK2-positive animals, suggest that a reduction of elevated leukocytes might be even more important for the prevention of thromboembolic events[6]. Furthermore, it cannot be excluded that erythrocytes from PV patients also have an increased tendency to clump.

Moreover, controlling the Hct to <0.45 has not been proven to have a positive impact on the overall risk of disease progression: A high phlebotomy rate of more than 4 per year is even associated with an increased

risk of thrombosis [7]. Marchioli *et al.* compared in a clinical trial with 365 PV-patients the occurrence of major thrombotic events between a low Hct (<0.45) and a high Hct (>0.45-0.50) group. A lower Hct of <0.45 led to significantly fewer thromboembolic events [8]. However, it is important to note, that WBC was significantly higher in the high-Hct group compared to the low-Hct group. No significant difference between the groups was seen in the platelet count, but there was a trend to lower platelets in the low-hematocrit arm of the trial.

This suggests that instead of the goal to achieve a maximum Hct of 0.45, an evaluation of a "thrombosis-risk-score" that takes into account various factors such as RBC, MCV, WBC, and platelets, may be considered.

Ginzburg and colleagues describe the complex regulation of iron metabolism in PV patients and possible consequences for future PV-therapy. Iron deficiency is the logical consequence of repeated phlebotomies and the desired effect to inhibit accelerated erythropoiesis. Furthermore, many PV patients are already iron deficient at time of diagnosis of the disease [9]. Iron deficiency can cause manifold symptoms, which largely overlap with those of PV, especially the pruritus. Tammaro and colleagues hypothesized that iron deficiency might reduce the skin elasticity through a downregulation of gene expression encoding for fibrillin 1 and 3, thereby causing pruritus[10]. To reduce overall symptom burden, a normalization of the iron level would therefore be a desirable treatment goal in all PV patients.

MPNs have a tendency to progress from early stages (ET/PV) to more advanced stages (myelofibrosis or leukemia) in which the driving force for disease progression, as in many other cancers, is low-grade inflammation [11]. A continuously activated JAK-STAT-signaling is at least partly responsible for a pro-inflammatory milieu in the bone-marrow and periphery and might also be a cause for further genomic instability [12].

The ultimate therapeutic goal however, is to reduce chronic-inflammation, prevent thromboembolic events, minimize symptom burden and eliminate disease progression [13]. As the majority of PV patients has a long life expectancy, it is also important that the chronic treatment is well tolerated, with only moderate adverse-effects.

Treatment with interferon is known since decades to be able to normalize blood counts, to reduce JAK2-allele burden, to reduce symptom burden (especially reduce pruritus and elevated spleen size) and to induce a partial or complete hematologic and molecular remission at least in a subset of PV-patients [14]. Currently commercially available pegylated interferon is only administered once-a-week (interferon-α-2a, Pegasys®, average dosage 90 µg per week). A new form of fixed dose pegylated interferon (ropeginterferon α-2b, Besremi®) allows application at 14-day intervals [15]. It is currently the only interferon preparation approved in the EU for the treatment of PV.

However, the treatment with INF is often limited by severe adverse effects such as flue-like symptoms, fever, and the development of autoimmune diseases or depression. Even though many of these side effects are known to be clearly dose-dependent, a dose titration is limited due to ready-to-use syringes with fixed doses (i.e., 90 µg, 135 µg or 180 µg) [16]. We overcame this problem by dividing a 90 µg ready-to-use syringe into three aliquots à 30 µg/week, each subcutaneously applied through micro-insulin syringes (0.3 mm × 0.8; BD Micro-Fine).

In a clinical trial with 79 patients (40 PV and 39 ET) Quintás-Cardama and colleagues describe that treatment with normal doses of INF led to a complete hematological response (CHR) in 70% of all PV patients. The median time to achieve CHR was 47 days, ranging between 3 and 350 days. A complete or partial molecular response (CMR or PMR, respectively) with a reduction of the JAK2V617F-mutant allele burden, was achieved in 31% and 14%, respectively. Compared to CHR it took significantly longer to achieve CMR or PMR. The allele burden in PV patients decreased from a median of 64% before start of INF-treatment to 12% after 24 months and continued to decrease further after an additional follow-up period of 21 months. IFN was subcutaneously applied in a starting dose of 450 µg and based on poor tolerability reduced by 90 µg decrements to a dose of 90 µg weekly [17].

More recently, Pedersen et al. described the kinetics of the decline of JAK2-allele burden under INF-treatment. Based on their findings the authors vote for an early intervention with INF [18]. Even though we only treated with a fraction of the IFN dose described above, the results of our case report are in line with the results of Quintás-Cardama and Pederson [17]. However, whether a CMR can be achieved remains open. Due to the ongoing decline in hematopoiesis, we will increase the dose interval between the 30 µg injections of INF therapy in the next step.

Our results indicate that normalization of the iron status under INF therapy is possible, leading to a significant improvement in symptoms. As described above we recommend the development of a "thrombosis-risk-score" instead of the upper Hct-limit of < 0.45 as criterium. To enable an early intervention with ultra-low dose INF, pen applications would be required that allow adjustment for lower dosing.

With all limitations of a single case report, our results vote for starting the IFN treatment of PV patients with ultra-low dose INF as early as possible and titrate to the lowest required dose to normalize the hematological and molecular parameters instead of a fixed dose. We question, whether a "watch and wait" strategy with frequent phlebotomies, with the consequence of developing an iron deficiency anemia, are favorable for the further development of the disease.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTIONS

CD, JD and GB contributed equally in writing the case report. CN conducted genetic testing.

Ethics

Written informed consent of the patient was obtained for publication.

Data Availability

No data were used in this study.

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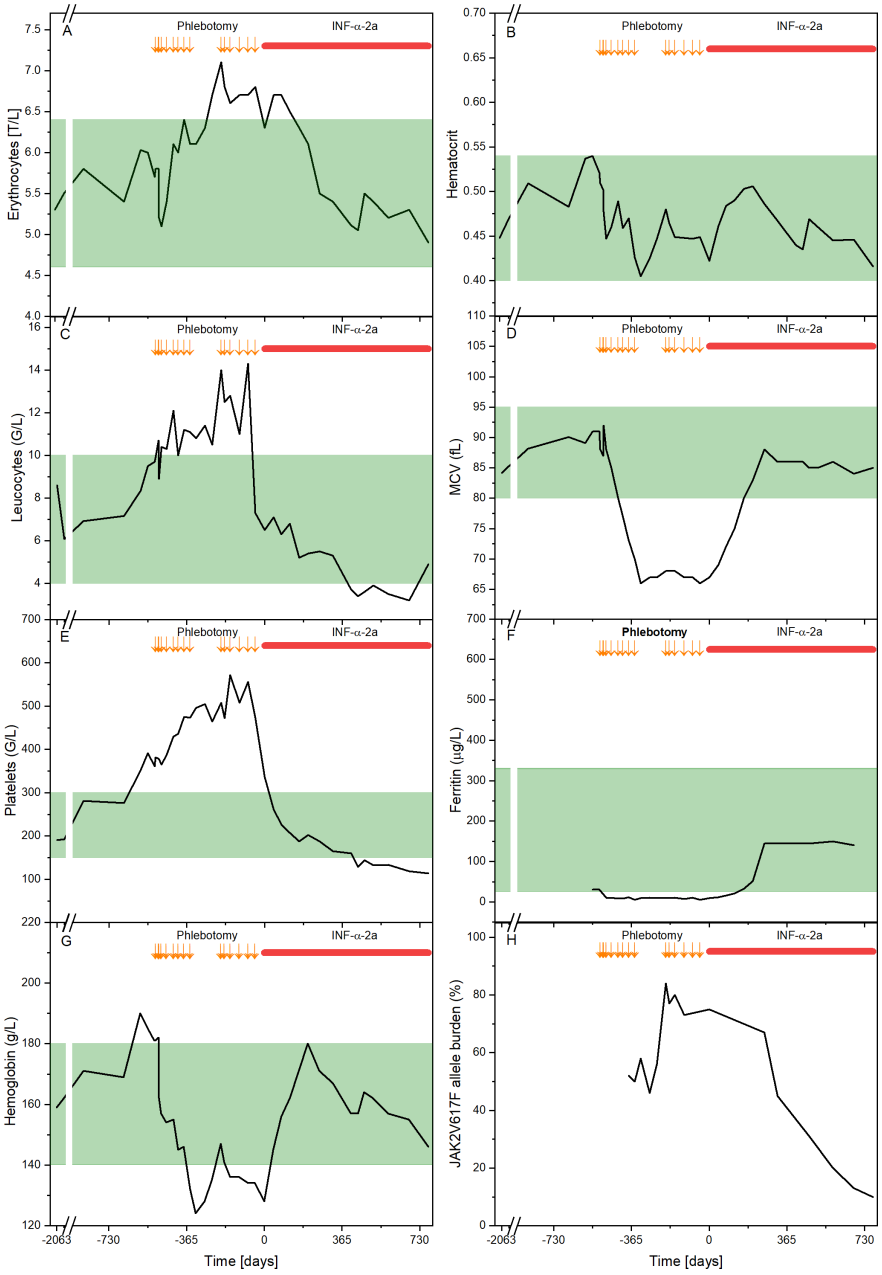
CONSENT STATEMENT

All the mentioned authors consent for publication.

Figure 1: Time-course of hematological parameters



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