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CASE REPORT

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

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Abstract

Low-dose interferon-α 2a treatment may be considered as an alternative to cytoreductive therapy with hydroxyurea or regularly dosed interferon in high-risk polycythemia vera patients.

KEYWORDS

interferon, low dose, polycythemia vera

1 | INTRODUCTION

Treatment of a high-risk polycythemia vera patient with low-dose interferon- α2a was well tolerated and resulted in complete hematologic and major molecular remission and a strong reduction of all symptoms, especially pruritus and fatigue.

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.[2]

2 | CASE PRESENTATION

We report a 50-year-old male patient with suspected PV, who presented himself in our hematological clinic in October 2017. He reported on first episodes of generalized aquagenic pruritus and two small vein thromboses in the posterior tibial and femoropopliteal veins in January and July 2017, respectively, both after long-distance flights. Furthermore, in connection with the second venous thrombosis, other elevated blood values appeared (Figure 1). The patient, who otherwise had a good health status, normal weight (BMI 22 kg/m^2) and was nonsmoker, was initially treated with the factor Xa-inhibitor rivaroxaban (Xarelto®, 20 mg OD). 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 tested to cover all the major myeloid disorders were found with the targeted NGS assay (Fisher Scientific AG). 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 had annual medical check-ups since 2013, the development of his blood values could be re-examined. The time-course of the hematological parameters is displayed in Figure 1.

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, treatment was started with phlebotomies (450 mL each), and in February 2018, the patient was switched from rivaroxaban to low-dose aspirin (75 mg morning / 50 mg evening). Under this therapy, a severe iron deficiency anemia developed (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, which showed an allele burden of 52% that remained 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, it was decided to switch the therapy to pegylated interferon- α2 (IFN- α-2a; Pegasys®) in January 2019. In order to improve initial tolerability,[3] treatment was started with a low dose of 30 μg/week. However, after only one month of treatment with IFN- α-2a, white blood cells (WBC) were back in the normal range and platelets were markedly reduced (Figure 1). It was decided, therefore, not to increase the dose. Parallel to the low-dose IFN- α-2a treatment a cautious oral iron substitution was started. In the course of further therapy, all blood values normalized and the low-dose aspirin was reduced from 125 mg/day to 1 × 100 mg/day.

Together with 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 July 2021, the JAK2V617F-allele burden decreased to 6% (Figure 1).

The treatment with 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.

3 | DISCUSSION

In high-risk patients, cytoreductive treatment with hydroxyurea or interferon is indicated (on average 150 μg/week (50–150 μg/week) according to the German Society of Haematology and Oncology[4]).

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.[5] 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.[6]

The ultimate therapeutic goal, however, is to reduce chronic-inflammation, prevent thromboembolic events, minimize symptom burden and eliminate disease progression.[7] 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 has been 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.[8] 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.[9] 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 flu-like symptoms, fever, and the development of autoimmune diseases or depression. Even though many of these side effects

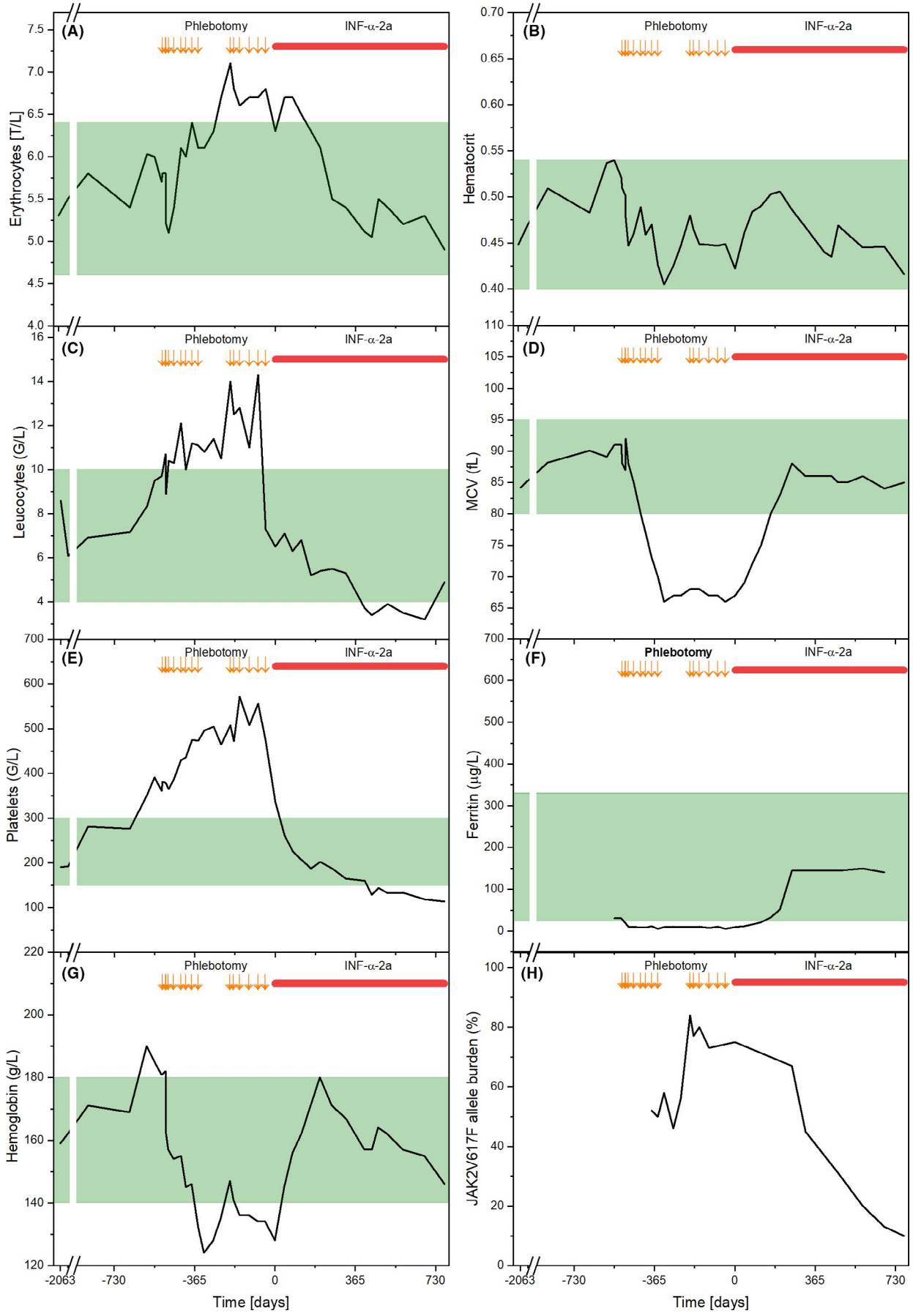

FIGURE 1 Time-course of hematological parameters

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).[10] This problem was overcome by dividing a 90 μg ready-to-use syringe into three aliquots à 30 μg/week; each subcutaneously applied by 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.[11]

More recently, Pedersen et al.[12] 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. 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.[11] 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.

We are aware that our technical approach is highly explorative and cannot be generalized. Further clinical studies are mandatory before clinical recommendations can be issued. However, our case report suggests the feasibility of a low-dose treatment and may motivate pharmaceutical companies to develop suitable pen-applications.

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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.

ETHICAL APPROVAL

Written informed consent of the patient was obtained for publication.

CONSENT

All the mentioned authors consent for publication.

DATA AVAILABILITY STATEMENT

No data were used in this study.

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