Clinical Case Reports

CASE REPORT

The impact of ruxolitinib treatment on inflammation-mediated comorbidities in myelofibrosis and related neoplasms

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Key clinical message

The inflammation-mediated comorbidities in myelofibrosis (MF) and related neoplasms (MPNs) likely reflect the concurrent immune deregulation and systemic inflammatory nature of the MPNs, emphasizing the link between chronic systemic inflammation, immune deregulation, and the malignant clone. JAK1-2 inhibitors in MF-patients reduce constitutional symptoms and splenomegaly, but also taget autoimmune and inflammation-mediated comorbidities.

Keywords

Autoimmunity, comorbidities, inflammation, myelofibrosis, myeloproliferative neoplasm, remission, ruxolitinib

Introduction

The classical Philadelphia negative chronic myeloproliferative neoplasms (MPNs) encompass mainly essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis [1]. These diseases are clonal, as evidenced by mutations such as the *JAK*2V617, *MPL*, and *CALR* [2–5]. The clinical MPN-phenotype is often accompanied by an inflammation-mediated comorbidity burden [6, 7]. This is most clearly demonstrated by the increased frequency of cardiovascular diseases, but also several other inflammatory diseases such as psoriasis, giant cell arteritis, and Crohn's disease [8, 9]. It has also been shown, that some rheumatological diseases increase the risk of hematological as well as non-hematological cancers, and that the risk of having a coincident second malignancy increases when suffering from an MPN [8–10]. Furthermore, patients with MPNs exhibit biochemical evidence of low-grade chronic inflammation as evidenced by elevated levels of C-reactive protein [11] and elevated levels of circulating YKL-40 [12, 13], which is considered a biomarker of chronic inflammation [14]. To this end, several inflammatory cytokines are elevated in patients with MPNs, in particular in myelofibrosis [15, 16]. Most recently, it has been shown that the elevated levels of cytokines are secreted by both malignant MPN-cells as well as nonmalignant cells [17] and that both subsets are affected by JAK inhibition. Furthermore, transcriptional profiling studies have unravelled a massive deregulation of inflammation and immune genes [18–22] - all supportive of the concept that disease progression in these neoplasms may at least partly be driven by chronic inflammation [6, 7, 16, 23] and concomitant immune deregulation [18–21, 24]. JAK-inhibitors have demonstrated anti-inflammatory and anti-proliferative potential. Consequently JAK-inhibitors are being extensively tested within several other areas, including dermatology and rheumatology [25–27]. The rationale in MPNs is the constitutively activated JAK-STAT signaling pathway giving rise to clonal myeloproliferation with an enhanced

proinflammatory cytokine profile, excessive formation of ROS, immune deregulation, and ultimately marrow fibrosis [2–7, 28, 29]. The cytokine profile is normalized in MF-patients during treatment with the JAK1-2 inhibitor ruxolitinib, and the clinical benefits for the majority of MF-patients are prompt with resolution of constitutional symptoms within days in concert with resolution of splenomegaly within months. The rapid improvement of constitutional symptoms is most likely attributed to normalization of the cytokine-profile [30–35].

Tofacitinib – a JAK1-3 inhibitor – is approved for the treatment of rheumatoid arthritis (RA) and phase 3 studies are ongoing investigating the role of JAK-inhibition in psoriasis. Furthermore, a topical form of ruxolitinib is being tested in the treatment of psoriasis, emphasizing the role for JAK-inhibitors in inflammatory and autoimmune diseases as well [25, 27]. In addition, a role in infectious diseases has also been suggested, indicated by the observation that ruxolitinib and tofacitinib – in vitro – inhibits HIV-1 [36].

Importantly, none of these inhibitors are strictly selective. They are rather promiscuous in nature and both have some activity with all the 3 different JAK's, their activities applying to both mutated and wild-type JAK's. This promiscuity explains the great potential in targeting several crucial points in MPN disease and inflammation-mediated comorbidities [37]. This phenomenon has recently been described in a few cases [38–40]. Herein, we wish to report on 3 additional patients suffering from MPN and receiving ruxolitinib, who during therapy experienced rapid and profound resolution of their non-hematological comorbidities. The perspectives for ruxolitinib in future studies will also be discussed.

Case reports

Case 1 – porphyria cutanea tarda (PCT)

A 76-year-old female suffering from PMF had received treatment with hydroxycarbamide for 3 years and was started on ruxolitinib due to constitutional symptoms (unintended weight loss) and progressive splenomegaly. The JAK2 allelic burden was 40%. Prior to the PMF-diagnosis the patient had been treated with percutaneous coronary intervention due to a stenosis and also suffered from hypertension. Seven years before the diagnosis of PMF the patient was diagnosed with PCT and treated with phlebotomies. Within 3 months of ruxolitinib therapy the patient experienced total resolution of the PCT in concert with resolution of constitutional symptoms and subsequently experienced a weight gain (intended). The allelic burden declined over 2 years of therapy from 40%

to 21% at last follow-up, but the thrombocytopenia was worsened reaching 27×10^9/L as nadir at last follow-up but without any bleeding episodes. The detrimental effect on the platelets was accompanied by an increase in the hemoglobin and the patient remained transfusion-independent.

Case 2 –- polymyalgia rheumatica (PMR)

A 73-year-old male suffering from PV had received treatment with interferon-alpha2a (IFN) and was started on a combination therapy with IFN and ruxolitinib based on signs of progressive disease with a persisting need of phlebotomies combined with thrombocytopenia, JAK2 allelic burden reaching 96%, constitutional symptoms (unintended weight loss) and progressive splenomegaly. Thus, the patient was likely in the transitional stage between PV and MF. Prior to ruxolitinib the patient had experienced deep vein thrombosis and paroxysmal atrial flutter. Two years prior to ruxolitinib therapy the patient had suffered from PMR and was treated in the rheumatological setting with steroids, which were associated with partial symptomatic improvement and a normalization of the sedimentation rate. Accordingly, it was concluded that the PMR was treated successfully and that the remaining symptoms (persisting morning stiffness and aches in the shoulder region) were due to age and not inflammatory activity. However, on treatment with ruxolitinib, the patient experienced a marked clinical improvement with disappearance of constitutional symptoms and – most remarkably – also total resolution of "age-related rheumatism" – the PMR-symptoms. This response was obtained in less than a month. The patient spontaneously expressed, that he now remembered the feeling of being healthy. Furthermore, both the hemoglobin levels and platelet counts initially dropped and subsequently increased during combination therapy, which was well tolerated.

Case 3 – psoriasis and psoriasis arthritis (PA)

A 61-year-old male suffering from post-PV-MF and intolerant to hydroxycarbamide and anagrelide was started on ruxolitinib due to progressive disease with constitutional symptoms and splenomegaly. The JAK2 allelic burden was 25%. The patient was also suffering from psoriasis and PA and was treated with sulfasalazine and methotrexate (MTX), but without proper disease control. The patient also suffered from severe hypertension receiving 4 different drugs to obtain normal blood-pressure. When the patient was started on ruxolitinib, the psoriasis lesions disappeared and itching virtually resolved as well. The arthritis also totally vanished within 3 weeks, and the methotrexate was discontinued without subsequent relapse of the arthritis.

The splenomegaly also totally resolved within 2 months and the *JAK2* allelic burden was reduced from the initial 25% to 5% within 7 months. The patient obtained a complete hematologic response within 2 months and the response was sustained at last follow-up after approximately 2 years of therapy. The patient stated that the therapy was the best that ever happened to him since he had also been able to start working again, which before ruxolitinib was impossible due to the severe constitutional symptoms, but also due to the severe psoriasis lesions in his hands which now had resolved. Furthermore, the patient experienced reduction of his blood-pressure, even below normal range. Consequently reduction and subsequent discontinuation of several of the anti-hypertensive drugs is ongoing with the hope of discontinuing them all.

Discussion

The highly impressive impact of ruxolitinib therapy on associated comorbidities in our patients reflects that JAK1-2 inhibition not only dampens the strict MPN-associated state with resolution of splenomegaly and constitutional symptoms but also – in general – has a huge impact upon MPN-associated inflammation-driven diseases as well. Thus, the common denominator for these diseases – chronic systemic inflammation and immune deregulation – is also being addressed by ruxolitinib therapy. Importantly, the successful outcome of ruxolitinib treatment in our patient with psoriasis also emphasizes that ruxolitinib may actually improve the performance status substantially and to a degree enabling the patient to start working again. Recently, this particular issue – the socioeconomic consequences for MPN-patients on ruxolitinib treatment – has been described [6]. Furthermore, the proposed improved survival in patients with myelofibrosis treated with ruxolitinib may likely be explained by improvement in inflammation-mediated comorbidities, which should also be carefully considered and addressed in future studies [6, 31, 33, 35].

The PCT case also illustrates the association (and in this case detrimental synergistic effect) between the inflammatory dermatological disorder and the MPN, accounting for increased cell counts and accordingly cell-turnover, thus challenging heme-metabolism beyond its natural boundaries. This happens in a patient already being stressed by an overwhelming immune-reaction towards photo-toxic metabolites accumulated over time due to insufficiency to metabolize heme within the normal range. In this setting, ruxolitinib addresses both the myeloproliferation, thereby reducing the amount of heme that has to be metabolized and also targets the inflammatory reaction towards the remaining photo-toxic heme-metabolites.

The PA case demonstrates several important aspects. Firstly, an important advantage of the anti-inflammatory potential of ruxolitinib is discontinuation or reduction in the use of disease modifying anti-rheumatic drugs (DMARD's), steroids and other medication prescribed for the nonmalignant inflammatory disease(s) accompanying MF. This is of major importance to the MF-patients since they are often thrombocytopenic and cannot handle further declines in platelet counts due to methotrexate treatment which is associated with many side-effects, including thrombocytopenia. Secondly, the ruxolitinib treatment is superior in regard to disease control in this patient, highlighting a possible role as 2nd line therapy in MTX-nonresponders [41]. Thirdly, a possible link between cardiovascular diseases and MPN – exemplified by hypertension – is demonstrated and apparently addressed by ruxolitinib therapy.

The PMR-case illustrates 2 important observations. Firstly the initial decline in platelet counts can be reversible during combination therapy – even in a thrombocytopenic patient receiving 2 drugs both having myelosuppressive potential. The subsequent increase in platelets is probably due to the reduced pooling and sequestration of platelets in the enlarged spleen [42], which resolves during ruxolitinib therapy. Secondly this case also substantiates the observation that combination therapy with ruxolitinib and IFN is feasible despite the theoretical concerns regarding safety and efficacy with combined therapy [43].

In conclusion, this report highlights the ability of ruxolitinib to improve the clinical course of MF-patients by alleviating their burden of comorbidities and also serves to illustrate the association between MPNs and inflammatory/autoimmune diseases. Further studies are urgently needed to substantiate our observations on several inflammation-driven diseases being efficaciously addressed by a single agent.

Conflict of Interest

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