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Case report

Sustained response off therapy after fostamatinib: A chronic refractory ITP case report

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ABSTRACT

Fostamatinib is a SYK-inhibitor drug recently approved by the FDA and EMA for treating chronic immune thrombocytopenia.

This drug induces a response in about 40% of patients and has a good toxicity profile. It is known that discontinuing thrombopoietin receptor agonists (TRAs) with the maintenance of sustained response off therapy is possible. On fostamatinib, we do not yet have such information.

In this case report, we describe the story of a woman with a multirefractory immune thrombocytopenia (steroids, splenectomy, rituximab, both available TRAs). After 16 years from diagnosis, she started fostamatinib therapy within a clinical trial and achieved a complete response. Grade 1–2 headache and diarrhea occurred during the first months of therapy. These adverse events were resolved with dose reduction of fostamatinib. Despite the dose reduction, the platelet count remained steadily above 80 $\times$ 10^9/L. After 4 years, fostamatinib was gradually reduced and finally discontinued with no drop in platelet count.

This is the first case in which fostamatinib discontinuation resulted in a sustained response off therapy.

1. Introduction

Primary Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by low platelet count ($<100 \times 10^9$/L) and increased bleeding risk [1,2].

One of the crucial mechanisms that induce thrombocytopenia is the Fc region of antiplatelet autoantibodies binding to Fc-gamma receptors on splenic macrophages, that activates the spleen tyrosine kinase (SYK) signaling pathway involved in the phagocytosis.

First line therapy includes steroids, IV immunoglobulin or platelet transfusions. Rituximab, splenectomy, and thrombopoietin receptor agonists (avatrombopag, eltrombopag, romiplostim), are available as second line therapies [3].

Fostamatinib is an orally bioavailable SYK inhibitor [4]. FIT1, FIT2 and the open-label extension FIT3 trials showed that fostamatinib may achieve a platelet response in around 40% of patients, with favorable safety profile [5–7]. Based on these results, fostamatinib was recently approved for chronic refractory ITP treatment.

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It has been shown that after obtaining a response with eltrombopag or romiplostim therapy, it can be achieved to maintain it even after their discontinuation, up to 30% of cases [8–10]. However, no data are yet available on the possibility to achieve a sustained response off therapy (SROT) with fostamatinib.

Here, we report a chronic refractory ITP case successfully treated with fostamatinib, which was subsequently discontinued without relapse.

2. Case presentation

In 1999, a 27-year-old female was referred to our Hematology because of isolated, severe thrombocytopenia (platelets: 3×10^9/L; leukocytes: 5.7×10^9/L with normal distribution, hemoglobin 11.5 g/dl) and mucocutaneous bleeding (Fig. 1).

ITP diagnosis was performed excluding other autoimmune or infective diseases and confirmed by a bone marrow biopsy.

Front-line, she received methylprednisolone (1 mg/kg for 28 days, then tapering and discontinuation in 4 months), achieving a complete response which was maintained until 2005.

Between 2005 and 2013, the patient experienced multiple relapses and was treated with dexamethasone, rituximab, azathioprine and danazol. Splenectomy was performed in 2011, obtaining a transient complete response.

At the beginning of 2013, she was treated with eltrombopag, then with romiplostim until March 2014, but both therapies were interrupted because of thrombocytosis and paresthesia without the achievement of a maintained complete response. At a subsequent relapse, a new administration of Rituximab 375 mg/kg was attempted, but the patient experienced an episode of anaphylaxis. Hence, low dose prednisone was administered to maintain at least a platelet count $>30 \times 10^9$ L.

In November 2015, she started fostamatinib/placebo, with low dose prednisone, after inclusion in the FIT2 study. During the earliest follow-up visits, mild adverse events (grade 1–2 headache and diarrhea) occurred and transient platelet responses were observed. In February 2016 the patient had severe thrombocytopenia requiring rescue therapy and was enrolled in the open label extension phase FIT3 trial. Fostamatinib was started at the dose of 100 mg bis in die (BID), which was reduced to 100 mg once a day in May 2016 due to grade 2 headache and diarrhea. After a dose reduction, both adverse events reduced to grade 1. The patient achieved a complete response after 4 weeks of fostamatinib; the response was maintained without significant platelet fluctuations during therapy.

In August 2019, fostamatinib was tapered to 100 mg every other day because of the persistence of grade 1 headache/diarrhea considering the long history of complete response. She maintained the complete response. In November 2019, fostamatinib was discontinued due to clinical trial end. Since fostamatinib discontinuation to the last follow-up, the patient has maintained a complete response without further ITP medication. To date, the duration of SROT is 24 months.

A transient platelet count dropping was reported only after the administration of anti-SarsCov2 BNT162b2 vaccine dose (from 200

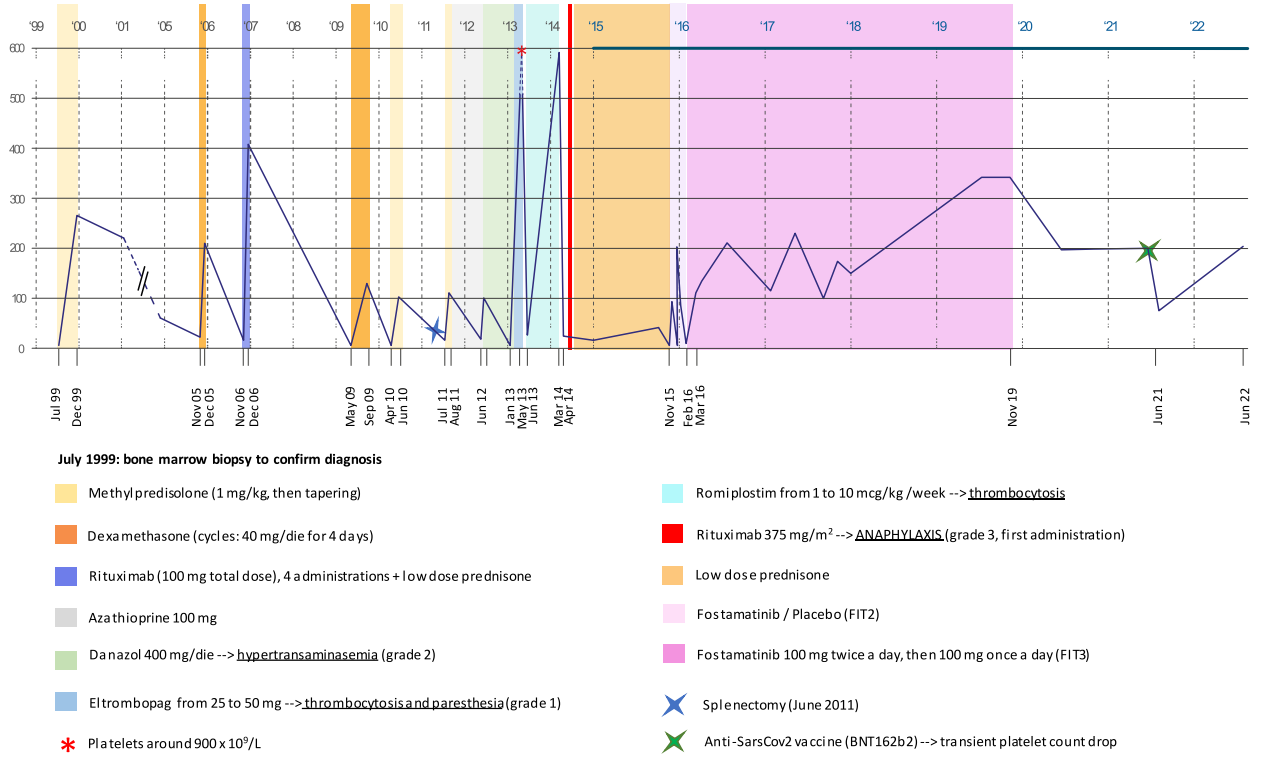

Fig. 1. Patient's storyline.

$\times 10^9$ L to 80 $\times 10^9$ L in June 2021), as previously reported in other patients [11]. The value of leukocytes and hemoglobin always remained normal. This platelet drop resolved spontaneously without any therapeutic intervention.

3. Discussion and conclusions

SROT is the possibility to discontinue "chronic" ITP treatment and maintain a safe platelet count for a prolonged time. Obtaining a SROT has become a key goal of ITP therapy. Previous studies have demonstrated that SROT may be achieved after splenectomy, rituximab, and thrombopoietin receptor agonists (TPO-RAs) eltrombopag/romiplostim [12–14]. It has been described TPO-RAs may modify the bone marrow immunological set-up, making the immune system tolerant to platelets [15,16]. The induction of this immune tolerance may allow the safe discontinuation of TPO-RAs.

We show for the first time that fostamatinib is also able to induce SROT. Notably, this result was achieved in a multi-refractory patient, with a history of ITP spanning more than a decade. The exact mechanisms of fostamatinib-induced SROT are still unknown. However, the inhibition of the Syk pathway results in a decreased autoimmune platelet clearance and in a decreased production of proinflammatory cytokines (IL-1β, IL-6, IL-8, TNF, and IL-10) from macrophages [17]. These are two possible mechanisms that support an immune modulatory effect of fostamatinib which may result in SROT.

Real-world data may further explore this important medical endpoint, and possibly identify predictors of SROT in fostamatinib-treated ITP patients.

Statement of ethics

Patient consent has been obtained from the patient.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

M.Ca acted as consultant and received honoraria from Jannsen, BMS Celgene, SanoFI, GlaxoSmithKline, Takeda, Amgen, Oncopeptides, AbbVie, Karyopharm, and Adaptive; Fr.Pa. consultancy and honoraria from Novartis, Celgene, AOP, Sierra Oncology and CTI; all other authors have no conflicts to declare.

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