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Synergistic effect of eltrombopag and deferasirox in aplastic anemia: a clinical case and review of the literature

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Severe Aplastic Anemia (SAA) is characterized by immune-mediated bone marrow hypoplasia and pancytopenia and can be effectively treated with immunosuppressive therapy [1], mainly based on antithymocyte globulin (ATG) and cyclosporine or with allogeneic stem cell transplantation [2]. One third of patients is refractory to immunosuppression, with persistent severe cytopenia and transfusion requirement [1].

Eltrombopag (ELT) is an orally bioavailable thrombopoietin receptor (TPO-R) agonist approved for the treatment of aplastic anemia after an insufficient response to initial immunosuppressive therapy.

Eltrombopag demonstrated activity as single-agent in this patient population, allowing up to 50% of patients to recover blood counts and to achieve transfusion independence thus confirming the clinical benefit of this approach [3,4].

Eltrombopag has also been combined to standard horse ATG plus cyclosporine in first line, resulting in impressive overall response rate, about 90%, and a complete response rate of 40% [5]. Interestingly, best results were observed when all drugs were started simultaneously [5].

Eltrombopag exhibits several actions on hematopoietic stem cells by distinct mechanisms, the main is related to the binding of TPO receptor C-MPL, but it is demonstrated that it activates other signaling pathways in megakaryocytes (MK) such as STAT3, ERK and AKT [6,7].

Furthermore, Eltrombopag, by binding the TPO receptor c-MPL, at a position distinct from the extracellular binding site of TPO, bypasses this inhibition induced by interferon-γ (IFN-γ), a pro-inflammatory cytokine, that is implicated in human hematopoietic stem and progenitor cell depletion in immune-mediated bone marrow failure syndromes [8].

It was shown that Eltrombopag, besides the known activity on the TPO receptor also decreases labile iron within the cells [9,10]. Eltrombopag chelates both extra and intra cellular calcium and iron and can shuttle iron out of cells. The iron chelating action of eltrombopag causes anti-proliferative effects on leukemic cells lines [11]. The chelation property can partially explain the differences observed between eltrombopag and other TPO mimetic drugs.

We report here a case of a patient affected by SAA who obtained complete hematological response when the irin chelator deferasirox was added to eltrombopag therapy.

Clinical case

A female patient, 67 yrs old, was diagnosed with SAA in June 2015. Her blood count was: white blood cells (WBC) 2.14 × 109/L, neutrophils 0.4 × 109/L, Hb 9 gr/dL, reticulocytes 20 × 109/L, platelets (PLT) 7 × 109/L, serum ferritin was 388 ng/mL. Virus infections by Hepatitis B (HBV) and C (HCV), Ebstein Barr (EBV), Cytomegalovirus (CMV), Parvovirus and Human Immunodeficiency Virus (HIV) were excluded. Anti nuclear antibodies and anti double strand DNA were negative. Bone marrow aspirate and biopsy showed a picture of aplastic anemia with an empty marrow and a cellularity less than 10%. Cytogenetic analysis was normal. She was treated with steroids and then with cyclosporine and four doses of

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thymoglobuline at the dose of 250 mg/day. After 4 months of immunosuppressive therapy the blood count was unchanged, the transfusion requirement was 4 platelets units and 6 RBC units/month. The serum ferritin was 3005 ng/mL, transferrin saturation was 57%. In September 2015 she started eltrombopag at escalating doses from 25 mg/day to 150 mg/day.

In December 2015, after 3 months of eltrombopag therapy the blood count was: WBC 3.4 × 109/L neutrophils 0.9 × 109/L, Hb 8,6 gr/dL, PLT 6 × 109/L. PLT transfusion requirement was stable and RBC transfusion requirement was slightly reduced (2 RBC U/month) and the serum ferritin level was 5506 ng/mL.

In December 2015 she started deferasirox at the dose of 10 mg/kg/day. After 1 month of deferasirox and eltrombopag therapy (January 2016) the WBC were 4.5 × 109/L, neutrophils 2.1 × 109/L, Hb 9,7 gr/dL, PLT 22 × 109/L. She obtained transfusion independence (Figure 1). The Hb and platelet counts progressively increased, in March 2016 the WBC were 4.4 × 109/L, Hb 11,2 gr/dL, PLT 29 × 109/L. In March 2016 she suspended Deferasirox for gastrointestinal intolerance. After 2 weeks of suspension the blood count was: WBC 2.8 × 109/L, neutrophils 0.87 × 109/L, Hb 8,2 gr/dL, PLT 12 × 109/L. She restarted transfusions of both RBC and PLT.

In May 2016 she restarted deferasirox at the dose of 10 mg/kg and she obtained again RBC and PLT transfusion independence and after 3 weeks the blood count was: WBC 3.66 × 109/L, neutrophils 1.3 × 109/L, Hb 11,2 gr/dL, PLT 31 × 109/L.

In July 2016, she discontinued deferasirox for gastrointestinal intolerance. After 2 weeks PLT and Hb decreased (PLT 13 × 109/L and Hb 9 gr/dL). She restarted deferasirox in and the blood count increased again and she obtained again transfusion independence.

From July 2016 until April 2017 the blood count progressively improved until completely normal values: WBC 6.9 × 109/L, neutrophils 3.1 × 109/L Hb 13,8 and PLT 152 × 109/L.

In July 2017 she stopped deferasirox when the serum ferritin was 501 ng/mL. In 2018 she progressively reduced eltrombopag dose from 150 mg to 25 mg/day.

At the moment we are writing, after 40 months of eltrombopag therapy and 18 months from deferasirox suspension the patient is in complete remission with a normal blood count.

She is currently under eltrombopag therapy at the dose of 25 mg twice a week. Her blood count is: WBC 6.76 × 109/L, neutrophils 3.68 × 109/L, Hb 14,1 gr/dL and PLT 201. × 109/L.

Hematological responses in patients with SAA have been reported during iron chelation therapy (ICT) in many studies [12–14]. In principle, some beneficial effects of eltrombopag on hematopoiesis in aplastic anemia, could also derive from its property to remove iron. Many case reports indicate that iron chelation can improve hematopoiesis. In 2008 Park and colleagues [12] reported a case of a 16-yr-old patient affected by SAA and secondary hemochromatosis due to red blood cell transfusions. He was diagnosed with aplastic anemia at 11-yr of age. After five years of transfusions he developed a dilated cardiomyopathy, multiple endocrine and liver dysfunction, generalized bleeding and and skin pigmentation. He started regular iron chelation therapy with deferoxamine, His cytopenia and organ dysfunctions gradually recovered until he completely normalized the peripheral blood cell

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count. Following these observations with deferoxamine many cases have been reported with oral iron chelator deferasirox.

In 2010 Koh and colleagues [13] reported two children with SAA and high transfusion requirement with iron overload who received iron chelation therapy with deferasirox. In one of them the restoration of trilineage hematopoiesis and consequent transfusion independence was observed in parallel with the reduction of serum ferritin level. In 2011 Lee and colleagues [14] reported a case of a child with SAA who, 7 years after diagnosis, was enrolled in a trial of iron chelation with deferasirox. He obtained a hematological improvement and transfusion independence.

In 2013 Lee and colleagues [15] reported the post hoc analysis of the EPIC trial, a prospective study enrolling patients with chronic anemia and iron overload due to chronic red blood cell transfusions.

The analysis was conducted on a sub-cohort of 116 patients with aplastic anemia. The hematologic responses were analyzed in 72 patients with evaluable hematologic parameters. Twenty-four patients received deferasirox without concomitant immunosuppressive treatment. Partial hematologic responses were observed in 11 of 24 (45.8%) patients; all became transfusion-independent. One patient had an additional platelet response and one patient had an additional platelet and hemoglobin response. The responses were associated with a significantly reduction of serum ferritin level.

At present, to the best of our knowledge, there are no cases reported in literature of patients with aplastic anemia treated with eltrombopag associated with deferasirox.

This case strongly suggests the possibility that deferasirox may improve eltrombopag response, probably by removing toxic iron. This observation requires further investigation but it may stimulate clinicians to pay attention to this effect.

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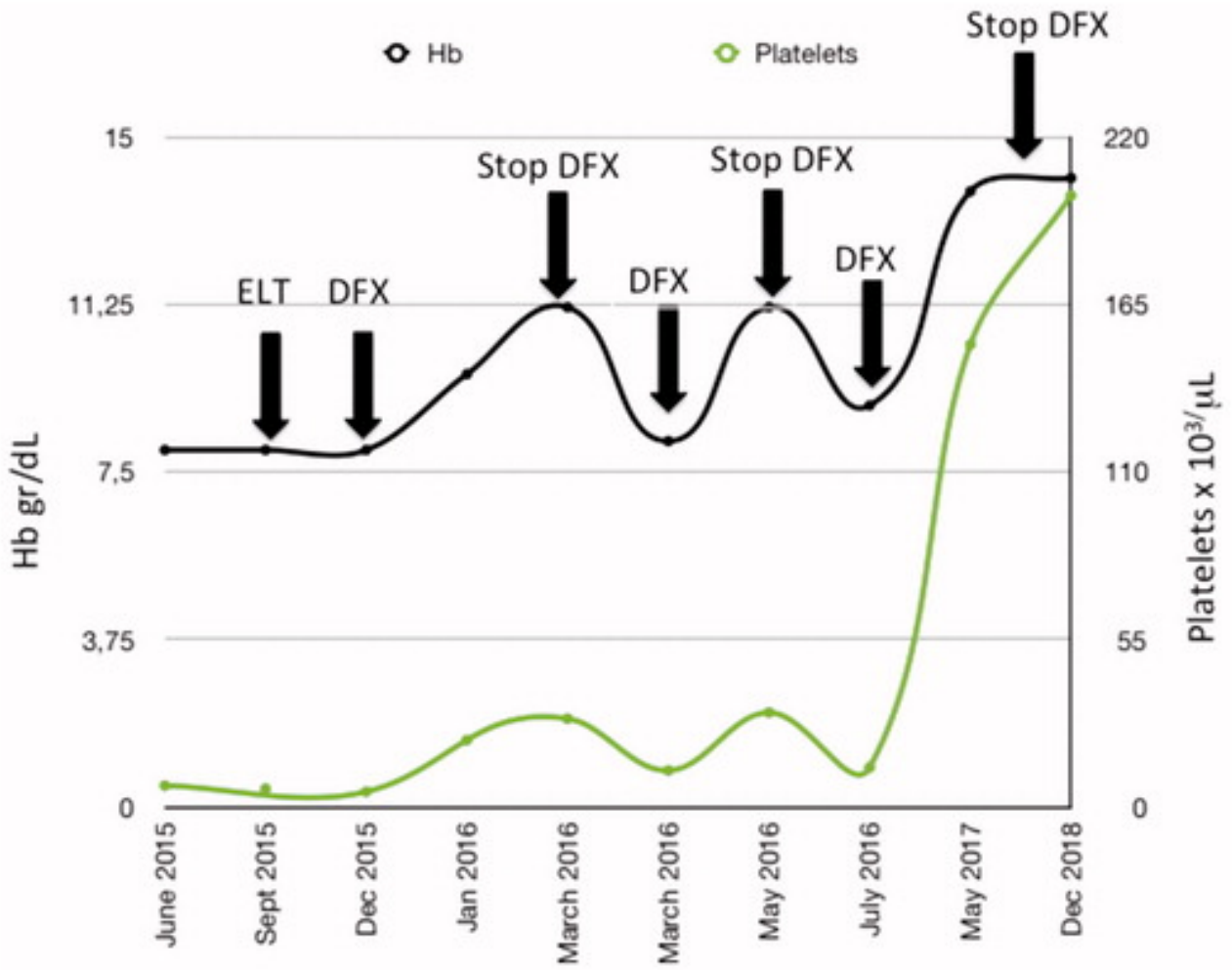
Figure 1. Hb and PLT count over time during eltrombopag (ELT) and deferasirox (DFX) therapy.



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Authors contributions
DC collected data and wrote the manuscript.

GA, MDr, MDe and GS collected data and provided final approval.

Disclosure statement
No potential conflict of interest was reported by the authors.

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