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CORRESPONDENCE

Rechallenging to Hydroxycarbamide Post Thalidomide Treatment and Response in a Non Transfusion-Dependent Patient, is it Possible?

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Dear Editor

The management of several patients with non transfusion dependent thalassaemia (NTDT) committed to receive regular blood transfusions may be cumbersome because of the occurrence of severe post-transfusion reactions and/or the development of irregular antibodies. We recently reported the case of an untransfusable patient that, because of the inefficacy of the long-term treatment with hydroxicarbamide (HU), was started on continuous low doses of thalidomide as off label therapy, obtaining the improvement in haemoglobin level and in a part of NTDT related complications [1]. Here we report the follow up data related to the interruption of thalidomide treatment, due to side effects, and to the re-challenging to HU.

Case Report

LMC is a 53-year-old female patient attending to our Thalassaemia Unit since she was 4 years old. She was 3-years-old when homozygous β-thalassaemia for β° 39 nonsense C → T mutation with a baseline haemoglobin almost completely (95%) represented by HbF was diagnosed; because of the presence of alpha-thalassaemia coinheritance, she showed a NTDT phenotype.

When she was 49-year-old (July 2012), following the loss of haematological response to HU treatment, she was treated for 40 months with thalidomide; as previously described, the prolonged gain in haemoglobin (Hb) level (from 4.8 to 9.0 g/d was also associated with interruption of chelation therapy and with major improvement in exercise tolerance and in quality of life. At the end of January 2016, under the continuous thalidomide administration, the patient had reached a further increase in haemoglobin level until to 10.7 g/dL, but because of the worsening of neuropathy (grade 3) at sural nerve and the occurrence of atrial flutter, we decided to discontinue thalidomide treatment. In March 2016, after 1 month of washout, the patient was restarted on HU 500 mg/d and thereafter 1000 mg/d. Her Hb level went down to 8.0 g/dL within the first month, reaching a haemoglobin nadir of 6.8 g/dL in May. Thereafter, in June her Hb reached 7.5 g/dL and currently she maintains a mean haemoglobin of 7.0 g/dL without signs of mielosuppression (Fig. 1). A normalization in the increase in eosinophil count (EO count) previously described during thalidomide treatment (from 9 to 1%) and an evident increase in mean corpuscular volume (MCV), from 75 to 105 fL, were observed (Fig. 1). Conversely, the levels of serum transferrin receptor (sTfR) slightly increased suggesting a poorer control of ineffective erythropoiesis [2, 3].

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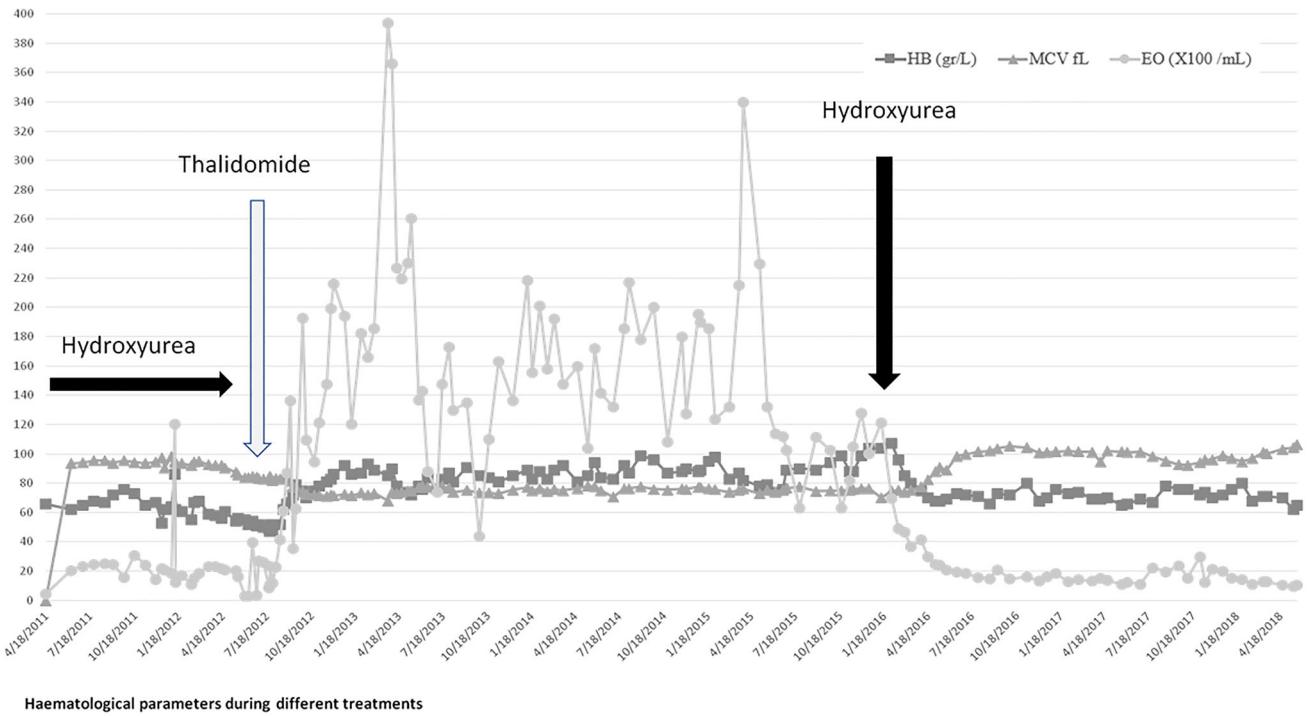

Fig. 1 Haematological parameters during different treatments

Discussion

HU is a drug with well-recognized and positive effects on Hb levels in NTDT patients but there is a paucity of data concerning the responsiveness and the duration of its response. In 2006 Mancuso et al. [4], in a small size study (24 patients) with a mean follow up of 66 months (range 3–144 months) reported a decrease in efficacy of HU treatment over time in four out of eleven responders. Thereafter, in a more detailed paper comprehensive of an "in vitro" evaluation, the same group showed that erythroid cultures obtained from patients during HU treatment reproduced the observed "in vivo response". In our previous report we found that the fall in efficacy of HU treatment was associated to the presence of a erythroid hyperplasia associated with conspicuous infiltration of Pseudo-Gaucher cell foamy macrophages; this histologic feature was markedly attenuated following thalidomide treatment [1]. Therefore, our current findings may lead to hypothesize also a negative impact of the long term treatment with HU on the overall bone marrow condition and in particular on macrophages function and on their ability as erythropoietin-complementary regulators of erythroid development [5]. Similarly, our current data on drop of eosinophil count to normal level, definitively indicate that its previous increase was a thalidomide-dependent effect and may suggest also a role of thalidomide in inducing the activation of stem cell factor (SCF), a growth factor involved also in regulating eosinophil number and function [6].

Treatment for patients with rare disease may involve the use of orphan or off-label drugs; it could be of interest to describe also possible delayed drug interactions [7]. These preliminary follow up data may suggest that haematological response to HU was restored following thalidomide treatment and interruption, likely reflecting a persistent amelioration in ineffective erythropoiesis. However, from a clinical point of view, thalidomide treatment represented a way to restore HU responsiveness maintaining adequate haemoglobin level in a patient that still was untransfusable; these data may suggest to test in a larger population of untransfusable NTDT patients the alternate use of both HU and thalidomide. Theoretically, a long term strategy based on shorter course of therapy, such as alternate day or month, to minimize specific drug toxicity and to further increase effectiveness of both drugs is hypothesizable.

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