Case Report

Agranulocyosis in Beta Thalassemia Major Patients treated with Oral Iron Chelating Agent (Deferiprone)

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Abstract

Deferiprone is an oral chelating agent that has been recently shown to reduce cardiac siderosis, but is also known to be associated with serious side effects like agranulocytosis which can be fatal. This report is a single centre experience of 5 cases with severe agranulocytosis in amongst 144 patients (3.47%) of thalassemia major on combined chelation therapy with subcutaneous desferrioxamine and oral deferiprone which is much higher than the previous reports.

Keywords: Thalassemia, Deferiprone, Granulocytosis.

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Introduction

The beta thalassemia syndrome is a group of hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. In the homozygous state, beta thalassemia may cause severe transfusion-dependent anemia (thalassaemia major).[1] The mainstay of treatment consists of hypertransfusion with packed red blood cells to maintain the patient's haemoglobin above 9-10 g/dL, thus improving the patient's sense of well-being while simultaneously suppressing ineffective erythropoiesis.[2] Unfortunately, this results in iron overload for which iron chelation therapy is needed to prevent damage to the heart, liver and endocrine glands. Until very recently, desferrioxamine has been the first-line drug of choice, but because of its cost in many countries and lack of compliance due to difficulty with administration, deferiprone (L1; CP20), the most extensively studied oral iron chelator to date[3] has emerged as suitable for patients for whom desferrioxamine is, for one reason or another, inadequate.[4] Another important issue that has favoured the use of deferiprone is a recent report that it is more effective in cardiac chelation.[5, 6] Deferiprone is an orally absorbed bidentate hydroxypyridinone iron chelator that induces urinary iron excretion.[7] The side effects of deferiprone (agranulocytosis, neutropenia, gastrointestinal symptoms, arthropathy, transient changes in liver enzymes, and zinc deficiency) are now well-recognized.[4, 8-13] They result in discontinuation of the drug in about 5–10% of patients.[14] However, some fatalities have also been reported.[15] Most studies show that the frequency of agranulocytosis is only about 0.5-0.6%.[7, 10, 16]

Here we report a series of 5 cases of severe agranulocytosis in one centre among 144 patients with thalassemia major on combined chelation therapy with subcutaneous desferrioxamine and oral deferiprone.

Case series

The clinical and demographic data of the patients are shown in Table 1. It shows that two patients were found to have neutropenia on routine blood tests and were asymptomatic. Patient #4 had two episodes of agranulocytosis. In the first episode, the patient presented with sepsis and agranulocytosis that was treated with a third-generation cephalosporin and an aminoglycoside for 10 days. He responded well to the treatment and his counts recovered. Unfortunately, deferiprone was restarted and the patient had much more severe episode of sepsis associated with agranulocytosis. *Klebsiella pneumonia* was isolated from the blood. He was treated with piperacillin/tazobactam and an aminoglycoside, which was changed to imipenem thereafter. He remained neutropenic and sick for two weeks before showing a response to G-CSF.

Table 1: Demographic and clinical parameters of the reported cases.

No	Age (years)	Sex	Average pretreatment Hb	Chelation Combined/ single	S.ferittin Pre/post deferiprone	Duration of deferiprone use	Mean ANC nadir	Complication during agranulocytosis	Doses of G-CSF 10ug/kg/dose
1	15	F	8.5	Combined	2583/3128	3 months	0.03	Sepsis	6 doses
2	13	M	10	Combined	1902/1564	1 year	0.38	Nil	1 dose
3	6	F	7.5	Combined	1750/706	5 months	0.02	Sepsis	7 doses
4	4	M	8.5	Combined	1571/4692	10 months 5 months	0.00 0.00	sepsis Klebsiella pneumonia	10 doses only in the second episode
5	6	F	9.5	Combined	1384/2117	4 months	0.46	Nil	nil

The other two patients followed almost a similar course and one of them is discussed further.

A 6-year-old Omani girl was started on hypertransfusion at the age of 2-1/2 years to maintain a pretransfusion haemoglobin of > 10g/dL. Iron chelation was begun at the age of 5 years when her serum ferritin was 1750 ng/mL. Her chelation therapy comprised desferrioxamine 0.5 g, five days per week and deferiprone 75 mg/kg/day, divided into three doses. At that time, she had a normal white cell count, 7.2 x10^9/L, with an absolute neutrophil count (ANC) of 3.1 x10^9/L. Over the next four months, the patient maintained a normal WBC and ANC, and desferrioxamine was discontinued when her serum ferritin fell to 705 ng/mL.

In July 2005, 5 months after starting deferiprone, the child presented to the hospital with history of high-grade fever for two days and one day of vomiting associated with generalized body weakness. On examination, she was found to be sick-looking and febrile, with a temperature of 39.7°C. The rest of her clinical examination was normal. Her ANC was 0.019 x10^9/L and a diagnosis of deferiprone-induced agranulocytosis was made. She was treated with broad-spectrum antibiotics and G-CSF 150 µg/day for 7 days. All cultures and viral studies were found to be negative. She showed marked clinical improvement and her ANC reached 2.9 x10^9/L one week after therapy. The child was discharged on subcutaneous desferrioxamine 0.5 g/day, five days per week.

Discussion

The mechanisms by which deferiprone produces neutropenia in patients with thalassemia are not fully understood and although there are some studies that point toward an immune-mediated or toxic mechanism, there is no firm evidence for either.[7,14] It may depend partly on the dose of deferiprone, the iron load of the patient, the patient's ethnic group and/or the nature of the underlying disease.[17]

The higher incidence of severe agranulocytosis in our patients is possibly due to ethnic differences as mild neutropenia is not uncommon in the Omani population. Congenital benign neutropenia, also known as "ethnic neutropenia" is well-known in this region.[18, 19] In our hospital, we have an estimated prevalence of 20% of patients with ANC below 1x10^9/L or even below 0.5x10^9/L and are not symptomatic despite these low counts.[20] These patients respond well to any infections and the low counts are presumed to be due to increased margination of the neutrophils. A retrospective review of our patients showed none to have had an ANC <1.5 x10^9/L prior to starting deferiprone. However, we did notice a drop in the ANC the first two weeks after starting the drug. On continuation of treatment with deferiprone, the ANC returned to pretreatment levels.

Several studies and reports have shown that agranulocytosis develops after a short duration of deferiprone use, ranging from three months to one year.[12-17, 21] The current protocol of deferiprone use advises rigid adherence to weekly monitoring of blood counts and strict guidelines for interrupting or discontinuing therapy. This affects the quality of life of these patients with multiple hospital attendance and blood collections, and may not be appropriate for patients who have already finished their first year of deferiprone therapy. In our practice, we perform weekly counts for the first 2 months and thereafter monthly assessments at the time of blood transfusion. As our patients have to travel long distances, it is not practical to do weekly blood counts. However, the patients are given detailed counselling regarding any fever and are advised to stop deferiprone immediately if this occurs and to go to the nearest hospital.

Conclusion

We can conclude from our data, bearing in mind the main limitation of this case series which is the small sample size, that deferiprone can be safely used for iron chelation in thalassaemia major patients with iron overload, especially because it offers increased cardiac protection and improved survival, so long as the ANC is very strictly and regularly monitored. In this way, it is possible to detect the likelihood of developing a life-threatening complication early so that it can be avoided or measures can be taken to minimize the side effects and their outcomes.

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