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CASE REPORT

A case of transfusion independence in a patient with myelodysplastic syndrome using deferasirox, sustained for two years after stopping therapy

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ABSTRACT

Patients with myelodysplastic syndrome (MDS) experience clinical complications related to progressive marrow failure and have an increased risk of developing acute myeloid leukemia. Frequent red blood cell transfusion can lead to clinical iron overload and is associated with decreased survival in MDS patients. Iron chelation therapy reduces markers of iron overload and prevents end-organ damage.

Here, we present the case of a patient with low-risk MDS with transfusional iron overload. He was treated for 2 years with an oral iron chelator, deferasirox, and after 12 months of treatment, he experienced a hemoglobin increase of more than 50 g/L, becoming transfusion-independent. He has remained transfusion-independent, with a normal hemoglobin level, for more than 2 years since stopping chelation therapy. Hematologic and erythroid responses have previously been reported in MDS patients treated with iron chelation. The durability of our patient's response suggests that iron chelation might alter the natural history of MDS in some patients.

KEY WORDS

Myelodysplastic syndrome, iron overload, iron chelation

1. INTRODUCTION

Myelodysplastic syndrome (MDS) is a heterogeneous group of hematologic neoplasms characterized by cytopenia and dysplasia in one or more of the major myeloid cell lines[1]. It is thought to result from unregulated proliferation of clonal hematopoietic stem cells, leading to abnormal maturation of the myeloid lineage and apoptosis in many of the developing cells[1]. The incidence of MDS increases with age and is conservatively estimated to be greater than 20 per 100,000 in the population more than 70 years of age[2]. Patients with MDS have a variable clinical course, but many eventually experience complications related to progressive marrow failure and an increased risk of developing acute leukemia[3].

Iron overload frequently occurs in MDS patients receiving blood transfusions and is associated with decreased survival[4]. Iron chelation reduces serum ferritin and the liver concentration of iron, which are associated in retrospective studies with improved survival in patients with MDS[5–8]. Here, we present the case of an MDS patient who became transfusion-independent after starting deferasirox and who has maintained normal hemoglobin levels for more than 2 years after stopping that medication.

2. CASE DESCRIPTION

A 74-year-old man presented with fatigue and chronic macrocytic anemia (hemoglobin 94 g/L and mean cell volume 103.3 fL). He had no other significant comorbidities, and his only medication was a multivitamin. His initial physical examination was unremarkable. White blood cell count was 4.0×10^9/L with a normal differential, and platelet count was 284×10^9/L. Serum B_{12}, folate, ferritin, and thyroid-stimulating hormone were normal, as were liver enzymes.

The patient became progressively more anemic and required blood transfusions for symptoms at hemoglobin levels of less than 80 g/L, initially receiving 2 units of packed red blood cells (RBCs) every 4 weeks.

A bone-marrow aspirate and biopsy performed 4 months later revealed a hypercellular bone marrow with dysplastic changes in the erythroid lineage. Figure 1 shows representative dysplastic changes. Fewer than 3% blasts were identified, and a normal male karyotype was reported. The patient was diagnosed with MDS (World Health Organization subtype: refractory cytopenia with unilineage dysplasia, refractory anemia)[9]. His initial International Prognostic Scoring System score was 0 (low risk). He remained transfusion-dependent, receiving approximately 2 units of blood every 2–3 weeks. We initially considered treatment with erythropoietin,

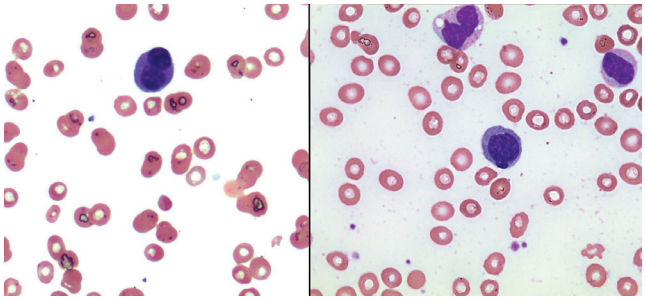

FIGURE 1 *Photomicrographs of representative dysplastic changes in an initial bone marrow aspirate. Left panel: Erythroid precursors with binucleate form. Right panel: Nuclear budding.*

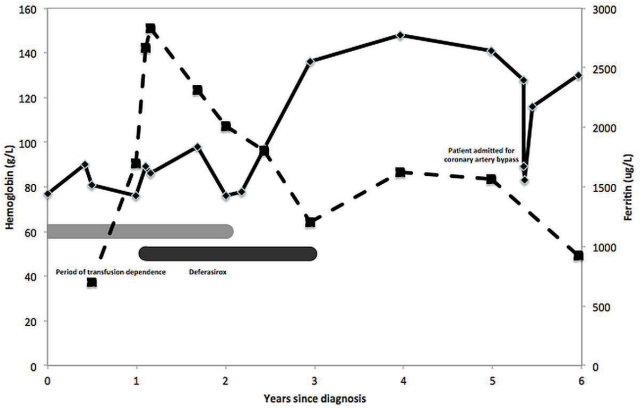

FIGURE 2 *Serum hemoglobin (solid line) and ferritin (broken line) levels over time. The solid grey bar indicates the period of transfusion-dependence. The solid black bar indicates the period of deferasirox use.*

but because the patient's serum erythropoietin level was greater than 500 U/L on several occasions, he did not qualify for government funding for that medication in our province.

After receiving more than 30 units of red-cell concentrates, the patient's serum ferritin reached 2668 µg/L, and he was started on oral deferasirox 1500 mg (20 mg/kg) daily. At 12 months after the start of iron chelation therapy, hemoglobin stabilized, and the patient no longer required transfusions. Before becoming transfusion-independent, he had received 92 units of packed RBCs over a 26-month period.

Deferasirox was stopped after approximately 2 years because the patient developed left eye episcleritis and was concerned that it might be an adverse effect of the medication. At that time, ferritin was 1500 µg/L, and hemoglobin was 149 g/L. The episcleritis did not improve with cessation of deferasirox, but the patient has not restarted the medication in the more than 2-year interval because he continues to feel well and has remained transfusion-independent. He has not taken any other treatments for the MDS, and his hemoglobin remains normal.

With the development of transfusion independence, the patient's quality of life has subjectively improved, with less fatigue and better exercise tolerance. Interestingly, the patient recently underwent coronary artery bypass surgery in the setting of a myocardial infarction, and during that admission, his hemoglobin dropped to 83 g/L, probably associated with surgical blood loss. He was not transfused at that time, and several months later, his hemoglobin had increased to 130 g/L. His most recent ferritin level (April 2014) was 925 µg/L, which, although elevated, is significantly lower than the level reported before the start of chelation. Figure 2 shows the patient's serial hemoglobin and ferritin levels.

3. DISCUSSION

Our case highlights the possibility that an improvement in erythropoiesis associated with iron chelation can be sustained over a long period. Several case descriptions[10,11] and published cohorts[12–18] have reported improved erythropoiesis and a decreased transfusion requirement in MDS patients treated with iron chelation.

In a prospective single-arm trial in 55 MDS patients using deferasirox, 16 patients (29.1%) were reported to have experienced an erythroid response as defined by International Working Group 2006 criteria[12,19]. In those 16 patients, the mean transfusion requirement at enrolment was 3.3 units monthly, which declined to 2.0 units monthly after 6 months of treatment and to 1.1 units monthly at 2 years[12].

A second trial of 173 low-risk to intermediate-1–risk MDS patients using deferasirox reported an erythroid response in 26 of 173 patients (15%), with a median time to response of 169 days (range: 84–382 days)[13].

A recent retrospective cohort described outcomes for 53 patients with transfusion-dependent MDS treated with deferasirox ($n = 36$) and deferoxamine ($n = 17$)[14]. The authors of that study reported that 19 patients (35.8%) experienced an erythroid response by International Working Group 2000 criteria[14,20]. Of those 19, 5 experienced a major erythroid response, with 3 becoming transfusion-independent; the remaining 14 experienced a minor erythroid response. The median time to response was 6 months (range: 3–21 months), and median duration of response was 12 months. All patients in the cohort with a major erythroid response maintained that response over the course of treatment, which was up to 21 months. The latter finding is notable because it parallels the experience of our patient, who also experienced a major erythroid response with prolonged transfusion independence. However, unlike our patient, the patients in the retrospective cohort continued to be treated with iron chelation for the duration of the reported response. A neutrophil and platelet response was also observed in some patients. Interestingly, the study authors reported that, on univariate analysis, an

increased transfusion burden and serum erythropoietin at baseline appeared to correlate with erythroid response to iron chelation. They found that each additional unit of RBCs transfused over a 3-month period resulted in a 16% increase in the odds of response ($p = 0.042$) and that each additional unit of serum erythropoietin resulted in a 0.2% increase in the odds of response ($p = 0.064$). Compared with diagnoses of refractory anemia or refractory cytopenia with unilineage dysplasia, a diagnosis of refractory anemia with ring sideroblasts was also associated with an increased likelihood of response: odds ratio 6.0 ($p = 0.013$) and odds ratio 12.6 ($p = 0.036$) respectively. The absolute reduction of serum ferritin after 1 year of iron chelation therapy was not significantly different for the patients with and without a hematologic improvement. Although ferritin is a crude marker for iron overload, the latter finding suggests that other individual or disease-related characteristics might be influencing the response to iron chelation.

A recent study reported improved erythropoiesis in a cohort of MDS patients ($n = 43$) and aplastic anemia patients ($n = 53$) treated with deferasirox over a 1-year period[15]. The mean hemoglobin level for the group had increased at the end of the study compared with baseline (7.62 ± 2.65 g/dL vs. 6.26 ± 0.94 g/dL, $p = 0.002$). Interestingly, the improvement was seen primarily in patients with aplastic anemia (+2.1 g/dL vs. +0.1 g/dL, $p = 0.01$). An improvement in platelet count was also observed in patients with aplastic anemia, although no increase in leucocyte count was apparent. Specific information about changes in transfusion requirements during the study period was not available. Approximately one third of the patients ($n = 31$) were receiving additional therapy for their disease during the study period, which might confound the interpretation of the data.

A *post hoc* analysis of the phase III, single-arm EPIC study reported on hematologic responses in a cohort of iron-overloaded MDS patients treated with deferasirox[18]. The authors of the study included patients with evaluable data from the EPIC trial who had not received other treatments. Using the International Working Group 2006 criteria, 21.5% (53 of 247 patients) experienced an erythroid response, 11.3% of which ($n = 28$) represented a transfusion-only erythroid response; 8.9% ($n = 22$), a hemoglobin-only erythroid response; and 1.2% ($n = 3$), a combined transfusion and hemoglobin response. A neutrophil response was experienced by 22% of patients (11 of 50), and a platelet response by 13% (13 of 100). The median time to response was 109 days (range: 1–286 days). Relapse after response occurred in 40% of the hemoglobin responders (10 of 25 patients), in 18% of the neutrophil responders (2 of 11 patients), and in 8% of the platelet responders (1 of 13 patients). Interestingly, serum ferritin declined more in hematologic responders than in non-responders, although the difference was not statistically significant.

Hematologic responses with iron chelation are not specific to deferasirox; responses were also reported with the use of deferoxamine in a cohort of MDS patients[16] and with the use of deferiprone in myelofibrosis[21]. Most prior publications about erythroid response with iron chelation in MDS have not reported whether stopping chelation is associated with loss of the erythroid response. Messa *et al.* reported a reduction in the transfusion requirement for a patient with primary myelofibrosis receiving deferasirox who subsequently lost the response after cessation of iron chelation[22]. Interestingly, the patient again experienced a reduced transfusion requirement with the resumption of iron chelation. Other reports of patients who have experienced sustained transfusion independence after stopping iron chelation have been published[16,23]. Di Tucci *et al.* described a patient with primary myelofibrosis who became transfusion-independent after approximately 5 months of treatment with deferasirox[23]. The patient stopped chelation after approximately 19 months of treatment, and the authors of the case report noted that transfusion independence continued for the following 2 years. Jensen *et al.* reported a series of 11 patients with MDS treated with deferoxamine, among whom 5 developed transfusion independence[16]. Of those 5 patients, 3 appeared to have sustained transfusion independence after stopping deferoxamine. Based on figures given in that publication, the duration of response after stopping chelation ranged from approximately 10 months to 40 months. Interestingly, one of the patients also appeared to have higher-risk MDS (World Health Organization diagnosis: refractory anemia with excess blasts).

The mechanisms underlying the improvement in transfusion requirement observed during treatment with iron chelators is largely unknown, but evidence suggests that the chelators can restore normal erythropoiesis and promote differentiation of hematopoietic precursors. A state of iron overload leads to increased formation of low-molecular-weight iron complexes or non-transferrin-bound iron, resulting in the formation of reactive oxygen species that oxidize proteins, lipids, and nucleic acid, with subsequent end-organ toxicity[24]. Oxidative DNA damage appears to be increased in patients with MDS, and it is plausible that partial reversal of this effect with iron chelation allows for greater genomic stability[25]. Elevated levels of non-transferrin-bound iron have been shown to correlate with markers of ineffective erythropoiesis such as abnormal bone marrow myeloid-to-erythroid ratios and increased apoptosis in MDS patients[26]. There is evidence that a transferrin saturation exceeding 80% predicts an elevated level of non-transferrin-bound iron, allowing transferrin saturation to be used as a marker of iron overload[27]. Although not validated in clinical practice, serial measurement of transferrin saturation might provide an indication of the state of oxidative stress in the

bone marrow microenvironment. Transferrin saturation measurements were not available in our patient, although they could potentially have provided additional information about the degree of iron overload and the effect of chelation.

In vitro experiments suggest that colony formation by erythroid burst-forming units is inversely related to serum ferritin in patients with MDS, providing additional evidence that iron overload might impair erythropoiesis[28,29]. This suppression of erythropoiesis appears to occur even at modestly elevated ferritin levels of more than 250 μg/L, and it is possible that iron chelation might help to reverse that effect[28]. Iron chelation can also effect the differentiation and proliferation of hematopoietic progenitors and blast cells[30,31]. Using an *in vitro* model of iron-overloaded bone marrow, Taoka *et al.*[30] reported that deferoxamine promotes differentiation of human stem cells into mature erythroblasts and that colony formation by erythroid burst-forming units was impaired at iron concentrations of 50 μmol/L. The addition of deferoxamine appeared to restore colony formation in a dose-dependent manner and to allow for differentiation into mature erythroid cells. In this set of experiments, iron overload also suppressed expression of the antiapoptotic gene *BCL2* and increased levels of reactive oxygen species and apoptosis.

The iron chelators deferasirox and deferoxamine have also been reported to promote the differentiation, *in vitro,* of acute myeloid leukemia cells toward the monocyte lineage[31]. Interestingly, the authors of the latter study reported the case of a patient with relapsed acute myeloid leukemia treated only with deferasirox and vitamin D, which led to decreased blast counts, an increased monocyte count, and partial reversal of cytopenias.

We hypothesize that, in our patient, iron chelation might have reset the balance for normal clonal expansion of hematopoietic stem cells with respect to their malignant counterparts in a way that could be sustained even after cessation of iron chelation.

4. CONCLUSIONS

In summary, our patient with low-risk MDS (International Prognostic Scoring System), transfusional iron overload from a transfusion burden of 92 units of RBCs, and a serum ferritin level of 2600 μg/L, became transfusion-independent 12 months after starting deferasirox (with no other intervention) and remains, remarkably, transfusion-independent more than 2 years after stopping the deferasirox—a change associated with subjective improvement in the patient's quality of life because of a decreased transfusion burden and a reduction in symptoms related to anemia.

We speculate that our patient's development of transfusion-independence has also lessened the risk of morbidity associated with chronic RBC transfusions and has likely lengthened his life expectancy. The hemoglobin normalization that has continued for more than 2 years after iron chelation therapy was stopped suggests the intriguing possibility that treatment of iron overload in MDS might alter the natural history of the disease in some patients. This interesting and potentially important phenomenon warrants further investigation and should be included as an endpoint in future clinical trials investigating iron chelation in MDS. An improved understanding of the mechanism underlying the observed improvement in erythropoiesis seen with iron chelation could allow for the identification of novel pathways that could be targeted in the treatment of MDS.

5. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest and CCH declares having served on advisory boards and having received honoraria as a speaker for Novartis, Celgene, Amgen, and Janssen. DS has no conflicts of interest to declare.

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