

CASE REPORT

Correction of anemia in a transfusion-dependent patient with primary myelofibrosis receiving iron chelation therapy with deferasirox (Exjade[®], ICL670)

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Abstract

Transfusional iron overload in patients with chronic anemias can result in multiple organ failure. Experience in the management of iron overload in patients with myelodysplastic syndromes is limited, as many do not receive chelation therapy due to short-life expectancy and the difficulties associated with the administration of the current reference standard chelator, deferoxamine. There have, however, been some reports of reduced transfusion requirement associated with chelation therapy in patients with myelodysplastic syndromes and myelofibrosis. Here, we discuss a patient with primary myelofibrosis and related transfusion-dependent anemia who received chelation therapy with the once-daily oral iron chelator, deferasirox. In addition to the reduced iron levels, the patient demonstrated an unexpected reduction in blood transfusion requirement, ultimately resulting in long-lasting transfusion-free survival.

Key words myelofibrosis; iron overload; chelation

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Case report

The patient (female) was diagnosed in March 2002 at the age of 61 with primary myelofibrosis (PMF) according to the World Health Organization diagnostic criteria (1). The initial symptom was fatigue. The disease was classified as 'intermediate risk' according to the prognostic classification of Dupriez *et al.* (LILLE system) (2), which is associated with a median survival of 26 months. From the time of diagnosis the patient's hemoglobin was 5–7 g/dL, necessitating packed red blood cell (PRBC) transfusions. The mean cellular volume was 78 fL and blood smear showed red cell poikilocytosis with dacryocytes. The Direct Coombs test was positive without any sign of hemolysis. There was mild thrombocytopenia (platelets $90 \times 10^3/\mu\text{L}$) and a normal white blood cell count; BCR/ABL was negative. Bone marrow

biopsy showed 20% cellularity with advanced stage of fibrosis, MF-2 according to Thiele *et al.* (3). From May 2002 to June 2003 the patient required approximately 2–3 PRBC units per month (total of 29 units) to maintain a pretransfusional hemoglobin level of 8.5 g/dL. In June 2003, the patient entered a phase II trial evaluating the efficacy and safety of once-daily oral chelator deferasirox in adults and children with a range of transfusion-dependent anemias. Baseline assessment of this patient (Table 1) showed that bone marrow cellularity had decreased to 10% with no modification in fibrosis score.

With dosing based on liver iron concentration, deferasirox was administered at 20 mg/kg/d for the duration of the 1-yr study. No other hematological therapy was administered during the study period.

Table 1 Patient's characteristics before chelation and after 1 yr of chelation therapy

	Baseline values prior to chelation (May 2002)	End of study (June 2003)
Hemoglobin (g/dL)	(transfusion therapy required)	12.5 (no transfusion therapy)
Reticulocytes (%)	1.8	1.0
Direct Coombs test	Positive	Negative
LIC (mg/g dw)	10.1	2.8
Serum ferritin ($\mu\text{g/L}$)	3001	1100
Transferrin saturation (%)	71	38
Bone marrow cellularity (%)	10	15
Fibrosis grading (3)	MF-2	MF-2
Teardrop cells (dacrocytes, %)	15	3
CD34+ (per μL)	16.4	11.1
Lactate/dehydrogenase (U/L)	530	438
Longitudinal diameter of spleen (cm)	13.5	12.0
Bone marrow iron	Present	Absent

LIC, liver iron concentration.

After 2 months of deferasirox therapy the patient's transfusion requirement progressively decreased (10 PRBC units were administered during the initial chelation therapy period) and transfusion therapy was ceased 5 months after study entry due to stable hemoglobin levels of 11.4–12.4 g/dL. At study end, liver iron concentration and serum ferritin levels were significantly reduced (Table 1). Re-evaluation of myelofibrosis by routine hematological evaluation and bone marrow biopsy revealed increased hemoglobin levels (12.5 g/dL), decreased CD34-positive cell counts, a negative Direct Coombs test, a reduction in teardrop cells, and normalization of mean corpuscular volume (90 fL). Bone marrow cellularity had increased to 15% with no modification in fibrosis score. Even if chelation therapy was not directly targeted to PMF a clinical improvement was obtained according to the international working group for myelofibrosis research and treatment response criteria (4). Due to the reduction in transfusions, deferasirox therapy was reduced to a dose of 5 mg/kg/d. Chelation therapy was finally interrupted in January 2005 when the patient's body iron content was within an acceptable range (serum ferritin 953 $\mu\text{g/L}$ and transferrin saturation 42%). To date (January 2007), the patient remains transfusion free (serum ferritin 499 $\mu\text{g/L}$ and transferrin saturation 34%), with a hemoglobin level of approximately 11 g/dL and normal hematological parameters (platelet count $120 \times 10^3/\mu\text{L}$).

Discussion

Primary myelofibrosis is an uncommon but severe condition associated with poor prognosis. For the majority of patients, therapy is palliative and many become transfusion dependent. Transfusion requirement often increases during the course of the disease due to collagen

deposition in the bone marrow and progressive impairment of erythropoiesis. The patient described here received iron chelation therapy as part of the clinical evaluation of oral deferasirox and experienced not only the anticipated fall in iron levels, but also an unexpected improvement in erythropoiesis. This improvement was so marked that the transfusion requirement decreased progressively and was ultimately deemed unnecessary, an effect that continued after cessation of chelation therapy. Clinical improvement (4) was evident as the patient became transfusion free, leading to a dramatic improvement in quality of life. This has been sustained to date (3 yr after cessation of transfusion requirement and more than 22 months after stopping chelation). Although iron chelation therapy has not been widely evaluated in patients with acquired anemia, reports have shown an improvement in bone marrow function in patients with myelodysplastic syndromes receiving deferoxamine (5) and in a patient with PMF receiving deferiprone (6). A variety of mechanisms are possible in different diseases (7), those postulated include: a limited cyto-reductive effect (5), iron redistribution to the hemopoietic tissue (8), ferrokinetic changes (9), suppression of increased apoptosis, and mitochondrial damage secondary to intracellular iron deposition (as it has been demonstrated that iron chelators can pass the erythroblast membrane) (10). Because of the persistent effect after chelation withdrawal, the latter appears to be the most promising mechanism to be investigated. Of course, a stochastic effect cannot be excluded, particularly in PMF in which a 'bizarre' behavior has been described (7), but the increasing number of similar reports in the literature support the need for a controlled clinical trial in transfusion-dependent acquired hemopoietic stem cell disorders to investigate the potential benefit of chelation on erythropoiesis.

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