Brief report

Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia

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A 10-year-old girl with steroid-resistant Diamond-Blackfan anemia (DBA) developed agranulocytosis 9 weeks after chelation with deferiprone was initiated (45 mg/kg daily, 60% of recommended dose) in addition to her ordinary deferoxamine therapy. The blood counts, checked weekly, dropped markedly between weeks 8 and 9. She rapidly developed a septicemia and was admitted with high fever (40.9°C), white blood cell count 0.4 × 10⁹/L, absolute neutrophil count 0.1 × 10⁹/L, and platelets 114 × 10⁹/L. She was administered broad spectrum antibiotics, G-CSF (10 microgram/kg daily) and corticosteroids but remained neutropenic and died 6 weeks after admission. Bone marrow examination day 23 revealed areas with low cellularity (around 30%), but also areas with infiltrates of T cells; granulopoiesis and erythropoiesis were scarce. We conclude that weekly neutrophil monitoring is not sufficient to avoid fatal agranulocytosis. We suggest that deferiprone not be prescribed to DBA patients unless the clinical indications are particularly strong, and that the risk of agranulocytosis in thalassemia patients be carefully considered. (Blood. 2007;109:5157-5159)

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Results and discussion

Case report

A 2-month-old girl born to healthy related parents was diagnosed with DBA (hemoglobin 27 g/L, white blood cell (WBC) count 14.1 × 10⁹/L, platelets 746 × 10⁹/L, reticulocytes 0.0% at admission). Bone marrow examination revealed an almost complete lack of erythropoiesis, consistent with DBA. She had no external malformations; ultrasound of the kidneys and skeletal survey were normal. In addition to erythocyte transfusions, she was administered prednisolone up to 4 mg/kg daily without any response. HSCT was considered, but she had no matched related donor and an unrelated donor transplant was at that time not recommended. Up to the age of 10 she was on a regular transfusion-chelating program with good compliance and ferritin levels typically between 1000-2000 microgram/L. A third prednisolone trial was not successful, nor was an attempt with cyclosporin A. Audiometry, normal at age 4, revealed a severe left side sensorineural hearing deficiency at age 6, the cause of which could not be fully explained. HSCT was reconsidered several times, but not accepted. Liver biopsies, performed at 3 and 6 years of age, revealed pronounced iron load and interstitial fibrosis but no cirrhosis.

The result of T2* MRI, performed at 10 years, was 21.3-28.2 msec in the heart (reference 16-20 msec) and 4.0-7.6 msec in the liver, clearly abnormal and below the lower normal reference of 17-19 msec. Ferritin was 2208 microgram/L. Her regular treatment was erythocyte transfusions (15 ml/kg) every second week and deferoxamine (750 mg) intravenously daily, corresponding to 34 mg/kg. Based on the abnormal T2* results, the liver biopsy findings of fibrosis, and high ferritin values despite regular deferoxamine therapy, deferiprone (Ferriprox®) 500 mg twice daily was added, corresponding to 60% of the recommended dose, in an attempt to reduce side effects. Blood counts were meticulously monitored on a weekly basis (Table 1). A secondary aim was to improve her quality of life. The parents were informed of the risk of agranulocytosis, which was the reason for the weekly blood count monitoring, and gave their consent to the therapy. Initially the deferiprone

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treatment was entirely successful, but the 9th week after initiating deferoxipone her blood counts dropped markedly to absolute neutrophil counts (ANC) less than 0.1 × 10^9/L, WBC 0.9 × 10^9/L and platelets 164 × 10^9/L; deferoxipone administration was stopped promptly (Table 1). However, by the following day she had developed a sore throat, moderate cough, and high fever (40.9°C) and was admitted with C-reactive protein (CRP) 37 mg/L, WBC 0.3 × 10^9/L, ANC 0.1 × 10^9/L and platelets 114 × 10^9/L.

Intravenous broad spectrum antibiotic therapy was initiated promptly, and the deferoxipone manufacturer was informed within a few days (April 2006). Pulmonary computed tomography (CT) reported 10-15 rounded infiltrates consistent with septic emboli, and blood culture revealed Staphylococcus aureus. Repeated echocardiograms revealed no signs of endocarditis. Filgrastim, 5 microgram per kg daily subcutaneously, was initiated soon after admission; from day 5 onwards 10 microgram per kg daily was administered. Her platelet counts (nadir 72 × 10^9/L day 2) were normalized to more than 150 × 10^9/L on day 6, but they declined again her last week of life (nadir 39 × 10^9/L). The WBC (nadir 0.2 × 10^9/L days 2 and 4) increased above 10^9/L on day 11 but dropped below 10^9/L day 23 and were never more than 0.5 × 10^9/L from day 30 onwards, except her last 2 days. Finally, her ANC remained at or below 0.1 × 10^9/L except for days 5, 19 and 20 (with 0.4 × 10^9/L at most; Figure 1).

On day 33, high doses of corticosteroids were introduced and on day 36 she was referred to the HSCT unit, afebrile and with CRP 7 mg/L. WBC 0.3 × 10^9/L, ANC less than 0.1 × 10^9/L and platelets 169 × 10^9/L. Despite the corticosteroids there was a trend with declining platelet counts, so cyclosporin A was tried. At day 42, while at home for the first time in a long while, she experienced increasing dyspnea, upper abdominal pains, and shivers. Examination at readmission showed an axillary temperature of 35.9°C, pulse 144, respiration rate 46 per minute and blood pressure 73/46 mmHg. Physical examination of the lungs and abdomen were reported as normal. CRP was 11 mg/L. The child had vomits, developing decreased saturation, and had a cardiac arrest. Resuscitation was initiated, but she died despite all efforts made at the ICU. The parents declined autopsy but approved postmortual CT, performed 13 hours after death. No conclusive cause of death could be obtained. Blood culture was negative.

Bone marrow examination on day 23 revealed variable cellularity with infiltrates of lymphocytes; between these infiltrates the cellularity was around 30% with signs of fibrosis. In areas with low cellularity, mostly macrophages and in particular megakaryocytes were found. Granulopoiesis and erythropoiesis was very scarce. The widely spread lymphoid infiltrates consisted mainly of a mixture of CD4+ and CD8+ T-cells; around the lymphoid infiltrates were a few polyclonal plasma cells. CD117 staining revealed a diffuse increase of mast cells. Bone marrow flow cytometry revealed that 72% of the cells were in the lymphocyte region: of these, 86% were T-cells with signs of activation and 57% stained for T-cell markers and HLADR. The CD4/CD8 ratio was 0.68. CD56+ cells were 21% and CD57+ cells 27%, the latter mostly CD8+CD28-. Furthermore, CD69+ T-cells were elevated (14%), indicating activation. CD34+ cells were 0.37% of all cells.

An updated review of PubMed (December 12, 2006) revealed one patient with DBA that developed agranulocytosis with deferoxipone.20 In the patient, a 28-year-old female, neutrophils reappeared after 17 days and normalized after 36 days. In addition, a 19-year-old male patient that developed neutropenia that was stable for one year but later progressed into a fatal aplastic anemia.21

| Table 1. Weekly blood counts from the introduction of deferoxipone until the agranulocytosis had developed. |
|----------------------------------|----------------------------------|-------------------|-------------------|
| Hemoglobin (g/L) | 109 | 81 | 93 | 73 | 91 | 70 | 84 | 105 | 83 | 87 |
| WBC (x10^9/L) | 5.4 | 3.7 | 4.0 | 3.9 | 5.5 | 3.8 | 3.7 | 4.6 | 2.5 | 0.9 |
| ANC (x10^9/L) | 3.7 | 2.4 | 2.7 | 2.6 | 4.0 | 2.6 | no data | 3.0 | 1.4 | 0.8 |
| Platelets (x10^9/L) | 272 | 273 | 274 | 227 | 263 | 222 | 170 | 278 | 208 | 151 |
| Ferritin (microgram/L) | 2027 | 1740 | 1986 | 1716 | 1491 |

§Values prior to start of deferoxipone therapy
*Erythrocyte transfusions 15 ml/kg body weight
#Deferiprone therapy was stopped this day and the patient was admitted to hospital the following day with septicemia
with signs of T-cell activation, suggests that immunological mechanisms may play a role in the development of the bone marrow hypoplasia in DBA. Thus, DBA patients may be more prone than thalassemia patients to developing deferiprone-associated agranulocytosis.

We conclude that since the agranulocytosis developed rapidly, weekly monitoring of blood counts during deferiprone therapy is not sufficient to avoid the development of persistent and potentially fatal agranulocytosis. Moreover, the rapid development of a prolonged agranulocytosis, despite administering only 60% of the recommended dose, suggests that this side effect may not be dose-dependent. Since the development of agranulocytosis is not predictable and possibly not dose-dependent, and since it is not avoidable despite meticulous blood count monitoring, we suggest that deferiprone not be prescribed to patients with DBA, or prescribed only if the clinical indications are particularly strong.

Data on the risk of agranulocytosis in thalassemia was updated in 2003 and additional information on deferiprone-associated agranulocytosis, available through the manufacturer, has now been presented (available through the website reported above). It is important that information regarding the risk of developing non-reversible agranulocytosis secondary to deferiprone, in particular in DBA patients, is widely distributed.

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Authorship

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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