Brief report

Hydroxyurea can eliminate transfusion requirements in children with severe β-thalassemia

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Hydroxyurea (HU) enhances fetal hemoglobin (Hb) production. An increase in total Hb level has been repeatedly reported during HU treatment in patients with sickle cell disease and in several patients with β-thalassemia intermedia. Effects in patients with β-thalassemia major are controversial. We now report a marked elevation of total Hb levels with HU that permitted regular transfusions to be stopped in 7 children with transfusion-dependent β-thalassemia. The median follow-up was 19 ± 3 months (range, 13-21 months). We conclude that HU can eliminate transfusional needs in children with β-thalassemia major, which could be particularly useful in countries such as Algeria, where supplies of blood or chelating agents are limited. (Blood. 2003;102:1529-1530)

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Introduction

Hydroxyurea (HU) promotes fetal hemoglobin (HbF) production via a reactivation of γ-genes as a result of molecular mechanisms that are not yet elucidated. The clinical benefit induced by this compound in patients affected with sickle cell disease has been repeatedly demonstrated.1,2 A significant benefit could also be expected in patients with β-thalassemia, because the imbalance in globin chains could be ameliorated by the newly synthesized γ-chains being able to neutralize the excess α-chains, which could partially correct ineffective erythropoiesis. Clinical and hematologic improvements have been reported in patients with thalassemia intermedia,3-8 but responses in patients with thalassemia major are controversial.5,9 We have followed 7 children with transfusion-dependent β-thalassemia, 6 of them with severe transfusional complications, and have treated them with hydroxyurea in the hope that this drug could reduce transfusional needs.

Study design

Seven children were included, 3 pairs of siblings and 1 single child. Their main clinical and biologic characteristics are given in Table 1. As blood supplies are limited in Algeria, the targeted post-transfusional hemoglobin level is only 70.0 to 90.0 g/L (7-9 g/dL). Six patients had major transfusional complications: transfusion-induced anaphylactic reactions (patient 1); severe chills and fever (patients 2, 6); post-transfusional complications: transfusion-induced anaphylactic reactions (patient 1); severe chills and fever (patients 2, 6); post-transfusional hemochromatosis (ferritin level, 3500 ng/mL) with cutaneous, hepatic, and gonadic manifestations (patient 3); multiple red cell alloimmunization (patient 4); and lack of venous access (patient 5). Patient 1 also had painful retroperitoneal masses, and scintigraphic and tomodensitometric studies attributed these masses to extramedullary hematopoesis. The parents of child 1 requested HU treatment for their other affected child (patient 7). The protocol was approved by the Hôpital Franz Fanon internal review board, and all families gave their informed consent.

Mean HU dose was 18.35 ± 2.1 mg/kg per day (range,15-20 mg/kg), given every day. Dosages were maximal at the start of treatment and were raised according to the children’s weight increase. HU treatment was begun at a mean of 34 ± 16 days (range, 15-65 days) after the last transfusion. Each month we determined complete blood counts (using the Sysmex 2000 counter [TOA Medical Electronics, Kobe, Japan]) and biochemical parameters, including blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels. HbF levels were calculated with the alkali denaturation technique (modified Betke method).

Results and discussion

The median follow-up was 19 months (range, 13-21 months) in October 2002. Total Hb increased in all patients, as indicated in Figure 1. In all patients, total Hb increased in the first month after beginning HU. Comparing initial and last values, mean Hb levels rose from 65.0 to 105.0 g/L (6.5-10.5 g/dL) in the 2 children with thalassemia intermedia, and from 45.0 ± 9.0 to 79.0 ± 8.0 g/L (4.5 ± 0.9 to 7.9 ± 0.8 g/dL) in the 5 children with thalassemia major. This increase permitted transfusions to be stopped in patients 1, 2, 3, 4, and 6. Patient 5 needed 2 erythrocyte concentrates after Hb fell to 47.0 g/L (4.7 g/dL) during a pulmonary infection. Patient 7 underwent splenectomy for hypersplenism 6 months after the beginning of HU and received 2 units of blood before splenectomy and 1 unit perioperatively. None of these patients have received further transfusions.

Mean corpuscular volume increased from 72 ± 3.5 to 87.4 ± 5.4 fl. Mean HbF increased from 90.9% ± 12.8% to 97.7% ± 2.1%. Mean circulating erythroblasts/100 leukocytes decreased from 149 400 ± 194 000 to 13 400 ± 12 300 (P = .01). All children
reported that they felt better and were more active. Median spleen size decreased in children without splenectomy from 6 to 3 cm. In addition, retroperitoneal masses observed in patient 1 regressed.

Clinical and hematologic safety was good. Increasing the HU dose to 25 mg/kg per day in patient 4 induced transient leukopenia. When the dose was decreased to 16.5 mg/kg per day, two patients noted nausea at the beginning of treatment, which resolved during follow-up, transfusions have been stopped in 2 patients, spaced out in 2 patients (1 every 2 months instead of 1 every month), and continued in 3 patients.

Moreover, the posttreatment Hb level (79.0 ± 8.0 g/L [7.9 ± 0.8 g/dL]) we observed in our children affected with thalassemia major is in fact within the target range defined in Algeria, but it is under the generally recommended post-transfusional Hb level in countries with sufficient blood supplies. However, we think it is important to emphasize that in some patients affected with severe β-thalassemia, HU raises total Hb levels while being well tolerated, at least in short- and medium-term use, and may represent a useful alternative to erythrocyte transfusions.

References