Hydroxyurea can eliminate transfusion requirements in children

with severe beta thalassemia

Hydroxyurea treatment in β-thalassemic children

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Abstract
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 seven transfusion-dependent β-thalassemic children. The median follow-up was 19 ± 3 months (range: 13-21). We conclude that HU can eliminate transfusional needs in children with β-thalassemia major, which could be particularly useful in countries like Algeria, where supplies of blood or chelating agents are limited.
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Introduction
Hydroxyurea (HU) promotes fetal hemoglobin (HbF) production via a reactivation of γ-genes, thanks to 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, since 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 hematological 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 up seven transfusion-dependent β-thalassemic children, 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 one single child. Their main clinical and biological characteristics are given in Table 1. As blood supplies are limited in Algeria, the targeted post-transfusional hemoglobin level is only 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 hemochromatosis (ferritin level: 3500 ng/ml) with cutaneous, hepatic and gonadic manifestations (patient 3); multiple red cell alloimmunization (patient 4); lack of venous access (patient 5). Patient 1 also had painful retroperitoneal masses, and scintigraphic and tomodensitometric studies attributed these to extramedullary hematopoiesis. The parents of child 1 requested HU treatment for their other affected child (patient 7). The protocol was approved by the Internal Review Board, and all families gave their informed consent.

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<th>Xmn polymorphism</th>
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<th>Age at 1st transfusion (months)</th>
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</table>

EC*: erythrocyte concentrate

Mean HU dose was 18.35 ± 2.1 mg/kg/d (range:15-20), 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 a mean of 34 ± 16 days (range: 15-65) after the last transfusion. Each month we determined complete blood counts (using the Sysmex 2000 counter) and biochemical parameters including BUN, creatinine, AST, ALT and alkaline phosphatase. HbF levels were calculated with the alkali denaturation technique (modified Betke method).

Results and discussion

The median follow-up was 19 months (13-21) in October 2002. Total Hb increased in all patients, as indicated in Fig.1.

In all patients, total Hb increased in the first month after beginning HU. Comparing initial and last values, mean Hb levels rose from 6.5 to 10.5 g/dl in the 2 children with thalassemia intermedia, and from 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 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 before splenectomy and 1 unit peroperatively. None of these patients have received further transfusions.
Mean corpuscular volume increased from $72 \pm 3.5$ to $87.4 \pm 5.4$ fl. Mean HbF increased from $90.9 \pm 12.8$ to $97.7 \pm 2.1\%$. Mean circulating erythroblasts/100 leukocytes decreased from $149\,400 \pm 194\,000$ to $13\,400 \pm 12\,300$ ($p: 0.01$). All children reported that they felt better and more active. Median spleen size decreased in nonsplenectomized children by from 6 to 3 cm. In addition, retroperitoneal masses observed in patient 1 regressed.

Clinical and hematological safety was good. Increasing the HU dose to 25 mg/kg/d in patient 4 induced transient leukopenia ($3.8 \times 10^9/l$) and thrombopenia ($89 \times 10^9/l$), which resolved when the dose was decreased to 16.5 mg/kg/d. Two patients noted nausea at the beginning of treatment which resolved spontaneously.

In conclusion, our series agrees with previous studies reporting clinical and hematological improvement with HU, and regression of extramedullary hematopoietic masses in β-thalassemia intermedia patients [7, 10]. HU has already been successfully used in an irregularly transfused patient with β-thalassemia major [11]. This report is, to our knowledge, the first one showing sustained discontinuation of transfusions after beginning treatment with HU in 5 children affected with severe β-thalassemia major. It is possible that the effect of HU on γ-globin expression is associated with the type of thalassemic mutation or the Gγ-158 C>T polymorphism (Xmn I). It is notable that our patients had similar increases in Hb level whatever their genotypes (β0 or β+ mutations, Xmn I polymorphism). In addition, the increase in total Hb level in our patients is probably not completely explained by the sole increase in HbF from 91 to 98%. A reduction in ineffective erythropoiesis is strongly suggested by the marked decrease in the number of circulating erythroblasts. B-thalassemia is a very heterogeneous group of diseases related to multiple mutations, and our observation cannot be generalized prematurely to all β-thalassemic syndromes. Since these initial promising results, seven more transfusion-dependent β-thalassemic children have been treated with HU. After only some months of follow-up, transfusions have been stopped in 2, spaced out in 2 (one every 2 months instead of one every month), and continued in 3. Moreover, the post-transfusional Hb level ($7.9 \pm 0.8$ g/dl) we observed in our children affected with thalassemia
major is in fact within the target range defined in Algeria, but 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


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