Hydroxyurea Therapy in Highly Unstable Hemoglobin Carriers

To the Editor:

Unstable hemoglobins (Hbs) are variants of adult Hbs that tend to precipitate and form insoluble inclusions (Heinz bodies) within the red blood cell (RBC) or RBC precursor. They induce a broad spectrum of manifestations from asymptomatic to severe hemolytic anemia and dyserythropoiesis. In case of severe hemolysis, treatment is not codified because of the rarity and diversity of molecular variants. We report for the first time, to our knowledge, the usefulness of hydroxyurea (HU) therapy in two highly unstable Hb carriers.

Patient 1. A 24-year-old man, without familial history, had experienced chronic hemolytic anemia since his earliest childhood. A diagnosis of highly unstable hemoglobin Perth a2 β2 32, Leu → Pro was made at the age of 5 and splenectomy was performed, which led to a moderate reduction in hemolysis. In October 1989, when he was referred to our department, baseline blood counts fluctuated between the following values: Hb from 10 to 11 g/dL, mean corpuscular volume (MCV) from 105 to 115 fL, white blood cell (WBC) count from 10 to 18 x 10^3/L, platelets from 810 to 1,220 x 10^9/L (optically confirmed), reticulocytes from 760 to 1,810 x 10^9/L, bilirubinemia from 60 to 80 mg/L. Hydroxyurea 2 g/d was started in December 1989 because the patient was considered to be at important thrombotic risk because of the conjunction of chronic anemia and thrombocytosis post splenectomy. After 16 months of treatment (March 1991) no recurrence of acute hemolytic episodes had occurred. The Hb level remained stable, platelets were <450 x 10^9/L, bilirubin <60 mg/L, Hb F increased from 2.1% to 32.7%, and the unstable component diminished from 12.3% to 3%. After March 1991, the patient refused further regular treatment and follow-up. In June 1991 he experienced an episode of thrombo-embolism at another hospital. Platelets were at 610,000/μL but at this moment, Hb F level was not measured. Since July 1991 the patient has been regularly treated by hydroxyurea 2 g/d. Hematologic values of December 1995 (Hb, platelets, Hb F, unstable component) were similar to those of March 1991 (Fig 1). No thrombo-embolic complication has occurred since HU was restarted.

Patient 2. A 31-year-old woman, with congenital absence of uterus, without familial history, had experienced severe hemolytic anemia since the age of 8 months. A splenectomy was performed without exact diagnosis at the age of 2. No improvement of hemolysis was observed after splenectomy. In 1977, a diagnosis of highly unstable hemoglobin in the RBCs was made (by the presence of Heinz bodies, isopropanol, and heat-stability tests). The clinical course was marked by hemolytic episodes linked to oxidative drugs intake, requiring RBC transfusions in 1977 and 1993. In July 1993, the patient was referred to our department for a new hemolytic episode linked to ascorbic acid absorption. A paravertebral tumor corresponding to extramedullary hematopoiesis (3 cm × 3 cm) and gallstones were discovered. Cholecystectomy was performed in December 1993. The Hb baseline value was 6.7 g/dL, MCV 85 fL, WBC count 16,800/μL, platelets 580,000/μL, bilirubin 20 mg/L, Hb F 6.6%. A new hemoglobin variant, not detectable by conventional electrophoretic techniques, was identified and the mutation characterised: Hb Templeuve a2 β2 139-140, Asn-Ala → Thr (manuscript in preparation). In September 1994 continuous treatment with hydroxyurea (1 g/d) was started. Complete disappearance of extramedullary hematopoiesis paravertebral tumor was obtained on control CT scan performed in June 95. At this time, Hb level had increased to 7.5 g/dL, MCV to 120 fL, Hb F to 27%, and platelet count had decreased to 280,000/μL.

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For the majority of patients with unstable Hb no treatment is usually required except treatment with folic acid and eviction of oxidative drugs. In the presence of severe hemolytic anemia, splenectomy is the most frequently used treatment. However, thrombo-embolic events can be observed spontaneously or after splenectomy. In the two patients presented here, HU was useful in reducing the thrombotic risk and also, in patient 2, in reducing extramedullary hematopoiesis. In addition, an improvement of Hb level in patient 2, a reduction of the unstable component in patient 1 and a moderate reduction of hemolysis in both patients was observed. This favorable effect was probably related to the increase in the proportion of Hb F and/or decrease in the unstable Hb level. In conclusion, treatment with HU could be an interesting approach in highly unstable Hb carriers, at least if they have a high HbF response to HU:

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REFERENCES

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