Effects of Hydroxyurea in a Population of Brazilian Patients With Sickle Cell Anemia

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Fetal hemoglobin (HbF) inhibits the polymerization of sickle hemoglobin, modulating the clinical features of sickle cell anemia (SCA). Hydroxyurea (HU) therapy can increase the HbF level, although its production can be influenced by genetic determinants. Twenty-two Brazilian SCA patients were evaluated over 5 years before and after HU use. We analyzed (1) βS haplotype; (2) patient characteristics; and (3) toxicity. No differences between age, sex, and HU response were observed. We found 40.9% of homozygous for Bantu haplotype, and, in contrasting to other trials, we observed HbF level increase in this group (3.84–9.08 g/dL, P = 0.003). Adverse effects were rare. Labyrinthitis was observed in 2 (9.10%) patients after HU use, although this complication had not been described before. Am. J. Hematol. 78:243–244, 2005. © 2005 Wiley-Liss, Inc.

Key words: fetal hemoglobin; hydroxyurea; βS haplotype; sickle cell anemia

INTRODUCTION

Sickling in sickle cell anemia (SCA) is caused by polymerization of deoxygenated hemoglobin S (HbS). Non-S hemoglobin, such as A2 or F (HbF), could influence the HbS polymerization. HbF levels differ markedly among SCA adult patients, and it has been known that patients with higher HbF level have fewer pain episodes and longer survival [1].

Hydroxyurea (HU) therapy has proven clinical benefit in SCA and polymorphisms linked to the βS globin gene (βS haplotype) have been considered as genetic markers that could explain the clinical and drug response to HU in SCA [2–4].

In order to identify if HU could interfere with HbF, Brazilian SCA patients being treated with HU were evaluated over 5 years. We analyzed (1) βS haplotype; (2) patient characteristics before and after HU; and (3) treatment toxicity.

MATERIALS AND METHODS

Twenty-two homozygous SCA patients (15 females and 7 males) were included in the study, their ages ranging from 18 to 46 years (mean, 25.59 ± 7.79 years). Written informed consent was obtained from all participants, and the UNIFESP ethics committee approved the study. Patients were made aware of all risks associated with chronic exposure to HU, including risks of teratogenicity in pregnancy.

Patients over 18 years old with moderate to severe disease (at least three painful episodes in the year, previous acute chest syndrome, or recurrent crisis) met the basic criteria for entry into this trial. Reasons for trial exclusion were other sickle cell syndromes, pregnancy, drug abuse, long-term program of transfusion, stroke in the previous 6 years, human immunodeficiency virus, and bone marrow depression.

Patients were treated with HU as suggested by The Multicenter Study of Hydroxyurea [3,4] and received daily folic acid supplementation.

The patients were monitored monthly with complete blood count and reticulocytes. HbF was quantified

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bimonthly by alkali denaturation. DNA extraction was obtained from leukocytes, and haplotype analysis was performed as described by Sutton et al. [6]. Data obtained were analyzed by nonparametric statistical tests.

RESULTS

Twenty-two patients were followed for 12–60 months (mean, 30.45 months). Nine (40.90%) patients were homozygous for Bantu haplotype, 4 (18.18%) were homozygous for Benin, 7 (31.08%) were heterozygous Bantu–Benin haplotype, 1 (4.54%) had the Bantu-atypical haplotype, and 1 (4.54%) had the Benin-atypical haplotype.

The baseline HbF level was higher in Benin than Bantu patients, but this was not statistically significant (P = 0.251). We observed a significant increase in hemoglobin (Hb) when we considered all patients (P = 0.037). HbF levels, after treatment with HU, were also increased, but only the Bantu haplotype showed any statistical significance before and after treatment (Table I).

Neutropenic episodes were observed in 3 (13.63%) patients in weeks 20, 25, and 27, and they returned to the study after 5, 8, and 3 weeks, respectively. Myelotoxicity was observed in only 1 (4.54%) patient after 48 months of treatment, and 2 (9.09%) patients developed labyrinthitis after 13 and 15 months.

DISCUSSION

Several studies have been performed about determinants of response to HU such as βS haplotype [2–4,7–9]. In this study, we confirmed prior reports among the Brazilian population which showed a high incidence of Bantu haplotype, due to migration features of Brazilian black population [7,8].

We did not find any correlation between age, sex, and HU response. HU administration has been associated with clinical improvement, but a significant increase in the Hb level was not observed.

In contrast to previous reports, a significant increase in HbF level in Bantu patients after HU use was observed [3,4,8]. Perhaps this observation should be interpreted with caution due to the larger number of Bantu patients in our study.

The number of myelotoxic episodes in our study was lower than that reported in another series. Of particular interest, labyrinthitis was observed in 2 (9.10%) patients after more than 1 year of HU use, although this complication had not been described previously [3,4,9].

In conclusion, our study calls attention to the particular Bantu response to HU treatment compared with other trials. However, larger studies should be performed to clear up this question.

REFERENCES


TABLE I. Hemoglobin and Fetal Hemoglobin Values, Before and After Treatment With HU, of the 22 Patients Who Completed the Study

<table>
<thead>
<tr>
<th>Haplotype (N)</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (22)</td>
<td>5.02 ± 3.00</td>
<td>10.19 ± 5.00</td>
<td>0.0002</td>
</tr>
<tr>
<td>Bantu/Bantu (9)</td>
<td>3.84 ± 1.62</td>
<td>9.08 ± 4.20</td>
<td>0.003</td>
</tr>
<tr>
<td>Bantu/Benin (7)</td>
<td>6.46 ± 4.36</td>
<td>11.43 ± 5.31</td>
<td>0.059</td>
</tr>
<tr>
<td>Benin/Benin (4)</td>
<td>5.62 ± 2.87</td>
<td>10.32 ± 7.53</td>
<td>0.287</td>
</tr>
<tr>
<td>Bantu/atypical (1)</td>
<td>3.3</td>
<td>14.0</td>
<td>–</td>
</tr>
<tr>
<td>Benin/atypical (1)</td>
<td>5.1</td>
<td>7.1</td>
<td>–</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Hb (g/dL)</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (22)</td>
<td>7.91 ± 0.90</td>
<td>8.56 ± 1.10</td>
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</tr>
<tr>
<td>Bantu/Bantu (9)</td>
<td>8.04 ± 0.91</td>
<td>8.68 ± 1.26</td>
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<tr>
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<td>8.22 ± 0.88</td>
<td>8.62 ± 0.94</td>
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<td>7.27 ± 1.42</td>
<td>8.17 ± 1.50</td>
<td>0.417</td>
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<tr>
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<td>7.4</td>
<td>9.3</td>
<td>–</td>
</tr>
<tr>
<td>Benin/atypical (1)</td>
<td>7.7</td>
<td>7.8</td>
<td>–</td>
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