MORTALITY IN SICKLE CELL PATIENTS ON HYDROXYUREA THERAPY

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Word Counts:

Abstract: 148 words
Article: 1119 words

Scientific Heading: Red Cells

*Supported by NIH/NHLBI grant 1 RO1 HL 67682-01A1 (2001-2005)
Abstract

The efficacy of hydroxyurea (HU) and its role in the reduction in mortality in sickle cell patients has been established. However many patients still die from complications of this disease while on HU. Of the 226 patients treated with HU at our center, 38 died (34 of sickle cell-related causes). Acute chest syndrome (ACS) was the most common cause of death (35%). The deceased and surviving patients did not differ significantly in average HU dose, baseline Hb F, or maximum Hb F response. However, the deceased patients were significantly older when HU was instituted, were more anemic and more likely to have BAN or CAM haplotypes. They also had significantly higher serum BUN and creatinine. Sickle cell patients who die whilst on HU therapy may represent a subgroup of older patients, possibly with more severe disease and organ damage. Such patients need early identification and prompt HU institution.
**Introduction**

The mortality and morbidity in sickle cell disease (SCD) have been considerably reduced since the introduction of hydroxyurea in the 1990’s \(^{(1-3)}\). A recent update of the Multicenter Study of Hydroxyurea (MSH) showed that at nine years follow-up, patients who take HU have a 40% reduction in mortality compared to those who do not take the drug \(^{(4)}\). Despite the well-established ameliorative effects of HU, many adult SCD patients die of complications of the disease while on HU therapy \(^{(5)}\). Over the past 15 years, a large number of adult patients have been treated with HU at our center \(^{(6)}\). We now report the demographic, clinical and laboratory characteristics of the HU-treated deceased group, compared to HU-treated surviving patients.

**Methods**

A retrospective analysis of SCD patients who were followed at the Sickle Cell Center, Medical College of Georgia and treated with HU for a period of 1 to 180 months was performed. The indications for HU therapy included frequent vaso-occlusive crises (>3/year), severe anemia, acute chest syndrome, priapism, leg ulcers, and history of cerebrovascular accident. Hydroxyurea was started at a dose of 15mg/kg/day. Patients were kept on the same dose for at least two consecutive months and the dose was escalated by ~ 5 mg/kg according to the clinical response and to Hb F level achieved. Hematologic toxicity criteria and the precautions taken were the same as those for the MSH \(^{(3)}\). Patients were seen in the clinic monthly and lab analyses were performed, including complete blood count, chemistries, and Hb F quantitation by HPLC. Haplotyping was performed by Southern blot, dot-blot, and by sequencing of the \(^{\Delta} γ-IVS-II\).

Data are presented as mean ± SD except where otherwise stated. Student’s \(t\) test or Mann-Whitney \(U\) test was used to compare variables, as appropriate. Chi-square test was performed for
count data in the form of contingency tables. In addition, a logistic regression was performed with deceased as the dependent variable and the other parameters the independent variables. The correlation between maximum Hb F and total Hb in both groups were analyzed with linear regression.

Approval was obtained from the Human Assurance Committee for this study. Informed consent was provided according to the Declaration of Helsinki.

Results

Of the 226 (115 male, 111 female) SCD patients, aged 16-68 years, 38 (17 male, 21 female) were deceased at the time of the study. Of these 38 patients, 26 were on HU therapy at the time of death, and 12 were not compliant. The deceased group was older (mean age at the time of death=35.8 ±11.4 vs 32.1 ± 10.0 years for the surviving patients) at the time of analyses, but the difference was not significant p=0.07. The mean age when HU therapy was instituted was significantly higher in the deceased group (30.6 ± 11.3 years vs 26.4 ± 9.5 years, p=0.03). There was no significant difference between the deceased and survivors in terms of average HU dose (18.1 ± 3.8 mg/kg/day vs 18.2 ± 4.9 mg/kg/day, p=0.117) or duration of HU therapy (55.9 ± 31.6 vs 61.7 ± 35.0 months, p=0.4). Gender did not influence survival ($\chi^2$ =2.17, p=0.141). Four of the patients in the deceased group and five of the surviving group were participants in the MSH study.

When haplotype distribution (BAN, BEN, CAM, SEN) of the $\beta^+$ chromosomes in the deceased versus the surviving group was compared, it was found that patients with homozygous BAN or heterozygous CAM haplotypes were significantly more likely to be in the deceased
Table 1 summarizes the laboratory parameters pre-HU, the maximum value attained on HU (post-HU) and the difference between the two, for both the deceased and survivors. Pre-HU, the two groups differed significantly with regard to Hb (p=0.009), RBC (p=0.041) and creatinine (p=0.04). The variables that displayed a significant difference post-HU were RBC (p=0.013), MCV (p=0.006), MCH (p=0.015), WBC (p=0.029), BUN (p=0.011) and creatinine (p=0.001). The only variables that displayed significant differences between the pre- and post-HU values were Hb F (p=0.013), MCV (p=0.008) and MCH (p=0.026). Multivariate logistic regression showed that only post-HU RBC and BUN, 2 BAN alleles, or 1 CAM allele retained their significance. The correlation between maximum Hb F (%) attained with HU therapy and maximum total Hb (g/dl) is shown in Fig. 1. While there was a significant correlation between these values for the surviving group (r=0.35, p<0.0001), this was not the case for the deceased patients (r=0.14, p=0.4).

Of the 34 patients who died from sickle cell-related causes, 12 died from acute chest syndrome (ACS), 5 from multi-organ failure, 4 from stroke, 2 from end stage renal disease, and 1 each from cardiac arrest, sepsis, cardiac arrhythmia, and PE. In 7 patients, the cause of death could not be determined.

Discussion

As previously reported \(^{(1,2)}\), ACS remains the major cause of death among our patient population on HU (35%). It is of interest that while in surviving patients the haplotype distribution closely resembles that previously reported from Southeastern USA \(^{(8)}\), in the
deceased group, BAN and CAM haplotypes are over-represented. These observations are consistent with previous reports that BAN haplotype increases the risk of developing irreversible complications and worsens the prognosis\(^{(9,10)}\). It should be noted that in the MSH, the BAN haplotype also appeared to blunt the Hb F response to HU\(^{(11)}\). BUN and creatinine were significantly higher in the deceased group at baseline, and creatinine remained significantly higher at maximum response. It is noteworthy that in the deceased group, there is no significant correlation between the maximum Hb F achieved and the maximum total Hb under HU therapy. This is in contrast to the surviving group where there is a highly significant correlation between maximum Hb F response and maximum total Hb (p<0.0001), indicating a failure to translate the benefit from increased Hb F to a hematologic improvement, specifically, an improvement in anemia in the deceased patients (Fig. 1).

This study emphasizes the fact that HU is not effective in all SCD patients and those who die whilst on HU therapy may represent a subgroup of older patients, possibly with more severe disease and organ damage. Low pre-HU Hb, homozygous BAN and heterozygous CAM haplotypes could be indicators of poor outcome in SCD patients on HU. Alternative approaches that should be considered in this subgroup of patients include institution of HU therapy at earlier ages, administration of higher HU doses, and combination therapies particularly with erythropoietin since a potentiating effect has been described between the two\(^{(12,13)}\).

While neutrophil counts have been associated with adverse outcomes in other diseases besides SCD, we, like Steinberg et al\(^{(4)}\), could not demonstrate a relationship between neutrophil counts and mortality. Moreover, a significant fall in neutrophil counts as a result of HU therapy was observed in both deceased and surviving patients.
References


13. el-Hazmi MA, al-Momen A, Kandawamy S, Huraib S, Harakati M, al-Mohareb F, Warsy...
Table 1. Summary of Laboratory Values Pre- and Post-HU

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors</th>
<th></th>
<th></th>
<th></th>
<th>Deceased</th>
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<tbody>
<tr>
<td></td>
<td>Pre-HU</td>
<td>Post-HU</td>
<td>Difference</td>
<td>Pre-HU</td>
<td>Post-HU</td>
<td>Difference</td>
<td></td>
</tr>
<tr>
<td>Hb F%</td>
<td>5.8±4.3</td>
<td>18.5±9.3</td>
<td>12.7±8.5*</td>
<td>4.4±2.2</td>
<td>21.4±8.7</td>
<td>16.9±8.9</td>
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<tr>
<td>Hb F (g/dl)</td>
<td>0.5±0.4</td>
<td>1.8±1.0</td>
<td>1.2±0.9</td>
<td>0.4±0.2</td>
<td>2.0±1.0</td>
<td>1.5±0.9</td>
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<tr>
<td>Hb (g/dl)</td>
<td>8.4±1.3**</td>
<td>9.3±1.6</td>
<td>0.8±1.5</td>
<td>7.7±1.3</td>
<td>8.7±1.9</td>
<td>1.0±1.7</td>
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<tr>
<td>RBC x 10⁶/mm³</td>
<td>2.8±0.5*</td>
<td>2.5±0.5*</td>
<td>-0.3±0.5</td>
<td>2.5±0.7</td>
<td>2.3±0.7</td>
<td>-0.3±0.7</td>
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<tr>
<td>RDW %</td>
<td>21.8±3.8</td>
<td>18.9±3.9</td>
<td>-2.8±4.7</td>
<td>23.4±3.9</td>
<td>20.1±4.4</td>
<td>-3.1±5.5</td>
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<td>PCV</td>
<td>0.3±0.1</td>
<td>0.3±0.1</td>
<td>0.02±0.1</td>
<td>0.2±0.04</td>
<td>0.3±0.1</td>
<td>0.03±0.05</td>
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<td>Retics</td>
<td>287±130</td>
<td>167±110</td>
<td>-123±163</td>
<td>254±110</td>
<td>144±88.7</td>
<td>-108±151</td>
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<td>MCV (fl)</td>
<td>89.7±9.8</td>
<td>109±15.3**</td>
<td>18.8±12.7**</td>
<td>92.0±10.6</td>
<td>117±17.2</td>
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<td>MCH (pg)</td>
<td>30.9±3.8</td>
<td>37.1±5.4*</td>
<td>6.1±4.4*</td>
<td>31.7±4.4</td>
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<td>WBC x 10³/mm³</td>
<td>12.7±4.1</td>
<td>9.5±4.1*</td>
<td>-3.2±5.1</td>
<td>12.5±4.6</td>
<td>7.8±2.7</td>
<td>-4.7±5.3</td>
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<tr>
<td>Polys x 10³/mm³</td>
<td>7.2±3.5</td>
<td>5.1±3.1*</td>
<td>-2.1±3.9</td>
<td>7.0±3.9</td>
<td>3.9±1.8</td>
<td>-3.5±4.3</td>
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<td>Platelets</td>
<td>415±164</td>
<td>356±140</td>
<td>-64.7±152</td>
<td>447±147</td>
<td>379±177</td>
<td>-61±174.6</td>
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<tr>
<td>Bilirubin (mg/dl)</td>
<td>3.7±2.3</td>
<td>2.7±2.7</td>
<td>-1.1±2.3</td>
<td>3.1±1.9</td>
<td>2.1±2.4</td>
<td>-0.9±2.8</td>
<td></td>
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<tr>
<td>nRBC§</td>
<td>1.0±1.9</td>
<td>1.0±2.5</td>
<td>0.0±2.5</td>
<td>1.0±1.9</td>
<td>3.0±7.5</td>
<td>0.0±8.5</td>
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<tr>
<td>BUN§</td>
<td>7.0±1.5</td>
<td>7.0±1.5*</td>
<td>0.0±1.5</td>
<td>7.0±2.5</td>
<td>9.0±2.3</td>
<td>0.0±1.6</td>
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<tr>
<td>Creatinine§</td>
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<td>0.6±0.2**</td>
<td>0.0±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.0±0.2</td>
<td></td>
</tr>
</tbody>
</table>

* = significantly different from corresponding value for deceased group (p<0.05)

** = significantly different from corresponding value for deceased group (p<0.01)

§ = values are presented as median ± inter range
Figure 1. Correlation between maximum Hb F response and maximum total Hb achieved in surviving (Figure 1A) and deceased (Figure 1B) patients on HU.

Figure 1A. Surviving Patients: \( r = 0.35, r^2 = 0.12, p < 0.0001 \)

![Graph showing correlation between Hb F% and Hb g/dl for surviving patients](image)

Figure 1B. Deceased Patients: \( r = 0.14, r^2 = 0.02, p < 0.39973 \)

![Graph showing correlation between Hb F% and Hb g/dl for deceased patients](image)
Mortality in Sickle Cell Patients on Hydroxyurea Therapy

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