Brief report

Mortality in sickle cell patients on hydroxyurea therapy

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The efficacy of hydroxyurea (HU) and its role in the reduction in mortality in sickle cell patients has been established. Nevertheless, many patients still die of 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 (35%) cause of death. Deceased and surviving patients did not differ significantly in average HU dose, baseline fetal hemoglobin (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 blood-urea-nitrogen (BUN) and creatinine levels. Sickle cell patients who die while on HU therapy may represent a subgroup of older patients, possibly with more severe disease and more severe organ damage. Such patients need early identification and prompt HU institution. (Blood. 2005;105:545-547)

Introduction

Mortality and morbidity rates in sickle cell disease (SCD) have been considerably reduced since the introduction of hydroxyurea (HU) in the 1990s.[1-4] A recent update of the Multicenter Study of Hydroxyurea (MSH) showed that at 9 years' follow-up, the mortality rate among patients who take HU is reduced 40% compared with the rate among patients who do not take the drug.[5] Despite the well-established ameliorative effects of HU, many adult patients with SCD die of complications of the disease while on HU therapy.[6] During the past 15 years, a large number of adult patients have been treated with HU at our center.[7] We now report the demographic, clinical, and laboratory characteristics of the HU-treated deceased group compared with HU-treated surviving patients.

Study design

A retrospective analysis was performed of patients with SCD who were followed up at the Sickle Cell Center (Medical College of Georgia, Augusta) and were treated with HU for 1 to 180 months. Indications for HU therapy included frequent vaso-occlusive crises (> 3 per year), severe anemia, acute chest syndrome, priapism, leg ulcers, and history of cerebrovascular accident. Hydroxyurea was started at a dose of 15 mg/kg per day. Patients were kept on the same dose for at least 2 consecutive months, and the dose was escalated by approximately 5 mg/kg according to the clinical response and the fetal hemoglobin (Hb F) level achieved. Hematologic toxicity criteria and the precautions taken were the same as those of the MSH.[3] Patients were seen in the clinic monthly, and laboratory analyses were performed, including complete blood count, serum chemistry profiles, and Hb F quantitation by high-performance liquid chromatography (HPLC). Haplotyping was performed by Southern blot and dot-blot analyses and by sequencing of the $^{A}\gamma$–IVS-II.

Data are presented as mean ± SD except where otherwise stated. Student *t* test or Mann-Whitney *U* test was used to compare variables, as appropriate, and χ^2 analysis was performed for count data in the form of contingency tables. In addition, 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 was analyzed with linear regression.

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

Results and discussion

Of the 226 (115 male, 111 female) patients with SCD, aged 16 to 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 with therapy. The deceased group was older (mean age at 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 ($P = .07$). 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; $P = .03$). There was no significant difference between the deceased and survivors in terms of average HU dose (18.1 ± 3.8 mg/kg per day vs 18.2 ± 4.9 mg/kg per day; $P = .117$) or duration of HU therapy (55.9 ± 31.6 vs 61.7 ± 35.0 months; $P = .4$). Sex did not influence survival ($\chi^2 = 2.17$; $P = .141$). Four patients in the deceased group and 5 in the surviving group were participants in the MSH study.

When haplotype distributions (BAN, BEN, CAM, SEN) of the β^s chromosomes in the deceased and the surviving groups were compared, it was found that patients with homozygous BAN or heterozygous CAM haplotypes were significantly more likely to be

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Table 1. Summary of laboratory values before and after HU

Variable	Survivors			Deceased		
	Before HU	After HU	Difference	Before HU	After HU	Difference
Hb F, %	5.8 ± 4.3	18.5 ± 9.3	12.7 ± 8.5‡	4.4 ± 2.2	21.4 ± 8.7	16.9 ± 8.9
Hb F, g/dL	0.5 ± 0.4	1.8 ± 1.0	1.2 ± 0.9	0.4 ± 0.2	2.0 ± 1.0	1.5 ± 0.9
Hb, g/dL	8.4 ± 1.3†	9.3 ± 1.6	0.8 ± 1.5	7.7 ± 1.3	8.7 ± 1.9	1.0 ± 1.7
RBC × 10^6/mm^3	2.8 ± 0.5‡	2.5 ± 0.5‡	− 0.3 ± 0.5	2.5 ± 0.7	2.3 ± 0.7	− 0.3 ± 0.7
RDW, %	21.8 ± 3.8	18.9 ± 3.9	− 2.8 ± 4.7	23.4 ± 3.9	20.1 ± 4.4	− 3.1 ± 5.5
PCV	0.3 ± 0.1	0.3 ± 0.1	0.02 ± 0.1	0.2 ± 0.04	0.3 ± 0.1	0.03 ± 0.05
Retics	287 ± 130	167 ± 110	− 123 ± 163	254 ± 110	144 ± 88.7	− 108 ± 151
MCV, fL	89.7 ± 9.8	109 ± 15.3†	18.8 ± 12.7†	92.0 ± 10.6	117 ± 17.2	25.5 ± 11.5
MCH, pg	30.9 ± 3.8	37.1 ± 5.4‡	6.1 ± 4.4‡	31.7 ± 4.4	39.8 ± 6.2	8.1 ± 4.0
WBC × 10^3/mm^3	12.7 ± 4.1	9.5 ± 4.1‡	− 3.2 ± 5.1	12.5 ± 4.6	7.8 ± 2.7	− 4.7 ± 5.3
Polys × 10^3/mm^3	7.2 ± 3.5	5.1 ± 3.1‡	− 2.1 ± 3.9	7.0 ± 3.9	3.9 ± 1.8	− 3.5 ± 4.3
Platelets	415 ± 164	356 ± 140	− 64.7 ± 152	447 ± 147	379 ± 177	− 61 ± 174.6
Bilirubin, mg/dL	3.7 ± 2.3	2.7 ± 2.7	− 1.1 ± 2.3	3.1 ± 1.9	2.1 ± 2.4	− 0.9 ± 2.8
nRBC*	1.0 ± 1.9	1.0 ± 2.5	0.0 ± 2.5	1.0 ± 1.9	3.0 ± 7.5	0.0 ± 8.5
BUN*	7.0 ± 1.5	7.0 ± 1.5‡	0.0 ± 1.5	7.0 ± 2.5	9.0 ± 2.3	0.0 ± 1.6
Creatinine*	0.6 ± 0.2‡	0.6 ± 0.2†	0.0 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.0 ± 0.2

* Values are presented as median ± interrange.
† Significantly different from corresponding value for deceased group ($P < .01$).
‡ Significantly different from corresponding value for deceased group ($P < .05$).

in the deceased group (6.16, $P = .013$ for BAN −/− and +/− vs +/+; 5.71, $P = .017$ for CAM −/− vs +/−).

Table 1 summarizes the laboratory parameters before HU, the maximum value attained on HU (post-HU), and the difference between the 2, for the deceased and for survivors. Before HU, the 2 groups differed significantly with regard to Hb level ($P = .009$), red blood cell (RBC) count ($P = .041$), and creatinine ($P = .04$). Variables that displayed a significant difference after HU were RBCs ($P = .013$), mean corpuscular volume (MCV) ($P = .006$), mean corpuscular hemoglobin (MCH) ($P = .015$), white blood cell (WBC) count ($P = .029$), blood-urea-nitrogen (BUN) ($P = .011$), and creatinine ($P = .001$). The only variables that displayed significant differences between values before and after HU therapy were Hb F ($P = .013$), MCV ($P = .008$), and MCH ($P = .026$). Multivariate logistic regression showed that only post-HU RBCs and BUN, 2 BAN alleles, and 1 CAM allele retained their significance. The correlation between maximum Hb F (percentage) attained with HU therapy and maximum total Hb (g/dL) is shown in Figure 1. Although there was a significant correlation between these values for the surviving group ($r = 0.35$; $P < .0001$), this was not the case for the deceased patients ($r = 0.14$; $P = .4$).

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

As previously reported,[1,2] ACS remains the major cause of death among our patient population on HU (35%). Although in surviving patients the haplotype distribution closely resembles that previously reported from the southeastern United States,[8] in the deceased group, BAN and CAM haplotypes are overrepresented. These observations are consistent with previous reports that BAN haplotype increases the risk for 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. 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, in whom there is a highly significant correlation between maximum Hb F response and maximum total Hb ($P < .0001$), indicating a failure to translate the benefit from increased Hb F to a hematologic improvement, specifically an improvement in anemia in the deceased patients (Figure 1).

This study emphasizes the fact that HU is not effective in all patients with SCD, and those who die while on HU therapy may represent a subgroup of older patients, possibly with more severe disease and organ damage. Low Hb levels before HU therapy, homozygous BAN, and heterozygous CAM haplotypes could be indicators of poor outcomes in patients with SCD on HU. Alternative approaches that should be considered in this subgroup of patients include the institution of HU therapy at earlier ages, administration of higher HU doses, and combination therapies,

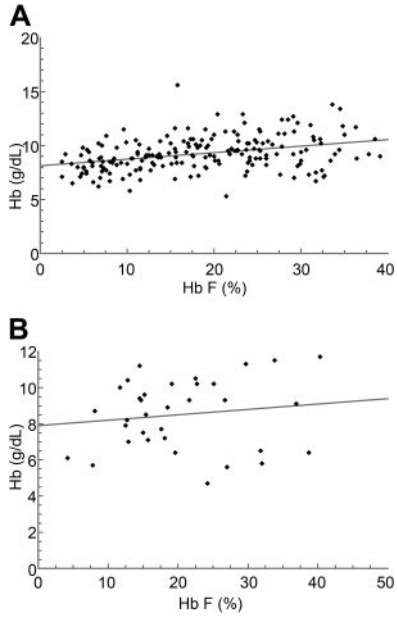

Figure 1. Correlation between maximum Hb F response and maximum total Hb achieved in surviving and deceased patients. (A) Surviving patients on HU: $r = 0.35$; $r^2 = 0.12$; $P < .0001$. (B) Deceased patients on HU: $r = 0.14$; $r^2 = 0.02$; $P = .39973$.

particularly with erythropoietin, because a potentiating effect has been described between the 2 agents.[12,13]

Although neutrophil counts have been associated with adverse outcomes in diseases other than SCD, we, like Steinberg et al,[5] could not demonstrate a relationship between neutrophil counts and mortality rates. Moreover, a significant decrease in neutrophil counts as a result of HU therapy was observed in deceased and surviving patients.

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