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A Retrospective Analysis of Sociodemographic and Hematologic Characteristics Associated with Achieving Optimal Hydroxyurea Therapy in Children with Sickle Cell Disease

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Abstract

Hydroxyurea (HU) has proven hematologic and clinical benefits, especially when escalated to the maximum tolerated dose (MTD). We reviewed clinical data from patients with sickle cell disease (SCD) (1/2011–1/2016) to determine baseline sociodemographic and laboratory parameters associated with reaching HU MTD without significant delays. 210 patients (mean HU start age=6.6 years) were included. Initial Kaplan-Meier event analysis showed 1 year to be an inflection point for reaching MTD. In total, 116 patients (55%) reached MTD in less than 1 year, with 56 (27%) taking greater than one year to reach MTD and 38 (18%) patients not successfully reaching MTD during follow up. In both crude and adjusted analyses, age at HU start was found to be significantly and inversely associated with reaching MTD within one year. The data presented, specifically the inflection point of reaching MTD at one year and the association of young HU start age with reaching MTD within a year, suggest that successful achievement of MTD will be facilitated by starting patients on HU at a young age and that older patients should receive additional intervention to attain MTD within one year. Patients who do not achieve MTD within a year may need the most extensive intervention.

Keywords

Sickle cell disease; Hydroxyurea; Pediatric; Maximum tolerated dose; Age

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1. Introduction

Sickle cell disease (SCD) is one of the most common monogenic disorders worldwide, with greater than 300,000 afflicted children born each year (1). The disease causes multi-system morbidity and a significant increase in overall mortality, with most SCD-related deaths occurring in childhood in low resource countries and in adulthood in high resource countries (2,3). One successful therapy for SCD is hydroxyurea (HU), a myelosuppressive agent and potent ribonucleotide reductase inhibitor. Though the exact mechanism remains incompletely understood, the majority of the clinical benefit of HU centers on its ability to increase the amount of fetal hemoglobin (HbF) in RBCs, thereby decreasing the fraction of intracellular HbS (4). Addition of HbF to the growing HbS polymer prevents further extension, reducing sickling, increasing RBC lifespan, and raising total hemoglobin (Hb) (5).

The clinical efficacy of HU therapy in patients with SCD has been well-validated in large, multi-center trials in both adult and pediatric populations (6–12). Hematologically, it has been demonstrated that HU causes significant increases in HbF and overall Hb with decreases in white blood cell (WBC) counts, absolute neutrophil counts (ANC), and reticulocyte counts (4,11,13–15). These increases in HbF and Hb and decreases in WBC and ANC have translated to better clinical outcomes; children on HU therapy have decreased rates of transfusions, pain crises, dactylitis, acute chest events, overall hospitalizations, and thus may lower overall mortality (8,11,13,16).

In an individual patient, the hematologic response to HU therapy has been demonstrated to be dose-dependent, with a higher HU dose resulting in higher HbF and Hb values (10,15–18). Importantly, HbF level is a prevailing predictor of the clinical severity of SCD, with low HbF levels associated with higher risk of early death (3,21). Further, a higher dose has not been associated with increased toxicity in adults, adolescents, or even very young children (8,14,17). Therefore, although a prospective trial has to date not been published comparing dosage, widely accepted practice is to treat patients with their maximum-tolerated dose (MTD) of hydroxyurea. In fact, National Heart, Lung, and Blood Institute SCD guidelines provide specific dose-escalation parameters (22). The principle behind MTD is that the HU dose is quickly escalated until bone marrow suppression becomes evident (typically when the ANC drops below $2.0\text{--}4.0 \times 10^3$ cells/microliter or absolute reticulocyte count (ARC) drops below $70\text{--}200 \times 10^9$ cells/liter) or when a pre-determined maximum HU dose is reached (typically between 30–35 mg/kg/day) (22).

Despite the large body of evidence for the efficacy and safety of HU at MTD, clinical experience demonstrates that a significant portion of patients with SCD, and especially pediatric patients, do not reach MTD or have a very prolonged escalation period. Drug adherence is the most commonly cited reason for non-escalation or cancellation of HU therapy (23,24). Thus, many patients on HU are not receiving optimal therapy at MTD. It is therefore of interest to identify the characteristics of patients who experience significant delays in reaching MTD or do not reach MTD, allowing prospective identification of patients at high risk for HU treatment failure or delay. Thus, the aims of the present study were to a) quantify the proportion of patients who reach MTD in an appropriate time frame,

defined as one year, among patients receiving HU at (blinded) and b) identify baseline hematologic and sociodemographic characteristics (*i.e.* characteristics at HU start) that are associated with successfully reaching MTD within this time frame.

2. Materials and Methods

Participants

The study was approved by the (blinded) Institutional Review Board. Patients were identified using a database consisting of all patients prescribed HU for sickle cell anemia (genotypes HbSS and HbS β^0 -thalassemia) between the ages of 6 months and 21 years of age at (blinded) and who had previously agreed to have their demographic information, laboratory results, and clinical course anonymously analyzed for research purposes. All patients prescribed HU were approached and > 99% agreed to participate. Patients were excluded from the analysis if: a) they had started HU prior to January 1, 2011 or after January 1, 2016; b) they had started HU at another institution or practice; c) they were lost to follow up within 1 year of starting HU.

Dependent Variable (time to MTD)

The aim of this study was to determine sociodemographic and hematologic characteristics associated with our dependent/outcome variable, time to MTD. Time to MTD is defined as the amount of time between the initial HU start date and the date at which MTD was achieved. The MTD date was the date at which the individual provider determined the patient had reached MTD. Data was collected via review of HU prescriptions and patient charts. At each visit the provider would indicate if HU dose escalation was warranted, with the following scenarios:

- a. If affirmative for HU escalation, the patient was determined to *not* be at MTD.
- b. If negative and the provider charted the patient was at MTD or patient was at a HU dose of 30 mg/kg/day or greater, the patient was determined to be at MTD.
- c. If negative and the provider indicated dose escalation would be warranted in the future, the patient was determined to *not* be at MTD.
- d. If negative for non-medical reasons (e.g., missed clinic appointments, missed HU doses), the patient was determined to *not* be at MTD.
- e. If negative with no reason provided, laboratory criteria were reviewed to determine whether the patient had reached MTD. If the patient's laboratory values were within parameters for having reached MTD (MTD definition of ANC between $2.0\text{--}4.0 \times 10^3$ cells/microliter and ARC $> 70\text{--}200 \times 10^9$ cells/liter) and no dose escalation at later dates occurred, the patient was determined to be at MTD.

Our institutional practice is to initiate HU at 20 mg/kg/day and to see patients again in 2 months for dose titration, typically a 5 mg/kg/day increase if target MTD is not reached, if the patient's laboratory values are within parameters for dose escalation (ANC $> 4.0 \times 10^3$

cells/microliter or $ARC > 70\text{--}200 \times 10^9$ cells/liter) and parents and patients report less than 5 missed doses. The maximum HU dose is 35 mg/kg/day.

Of note, each chart was reviewed until December 31, 2016 for HU dose escalation. Also, the date of the first prescribed dose of HU at the MTD dose was determined to be the date at which the patient had reached MTD.

Independent Variables

Hydroxyurea start age was defined as the age at which HU therapy was first initiated and was identified by chart review of provider notes and prescriptions. If patients started, stopped, and re-started HU therapy, the start age remained their initial start age and not subsequent re-start ages. Baseline (*i.e.* prior to HU initiation) laboratory values, including Hb, HbF, HbS, WBC, ANC, and ARC were collected on all patients; these lab results were readily available via chart review as it is institutional practice to collect these data prior to initiation of HU therapy. The independent variables, both socioeconomic and hematologic, were chosen *a priori*; specifically, Hb, HbF, HbS, WBC, ANC, and ARC were chosen as these are hematologic parameters that are both monitored and affect the clinical status of patients on HU therapy.

Statistical Analysis

We performed a survival analysis in which the outcome was time to MTD event (in years). We created a Kaplan-Meier curve using the complete sample ($n=210$). A critical time point at one year of follow up was detected in the Kaplan-Meier curve, which supported our *a priori* time-frame of one year based on the above clinical reasoning, and was used as a dichotomization point in our subsequent analyses.

The characteristics of participants were explored via means and standard deviations as well as simple frequencies and percentages, in the complete sample and after dichotomization by “reaching MTD within 1 year of HU therapy” ($n=116$) or “not reaching MTD within 1 year of HU therapy” ($n=94$). Dichotomist variables (sex, race and SCD genotype) were compared between both groups using a Fisher’s Exact test. Continuous variables (age, BMI, Hb, HbS, HbF, WBC, ANC and ARC; all measured at baseline) were analyzed by one-way ANOVA.

We then estimated crude and adjusted risk ratios (RR) of reaching MTD within 1 year, using simple and multiple log-Poisson robust models (25). First, we estimated crude RR for each baseline covariate of interest: sex, age, race, BMI, Hb type, Hb, HbS, HbF, WBC, ANC, and ARC. Next, we performed four models for obtaining adjusted RR and compared these models using Akaike Information Criterion (AIC). We started with null and full models, the last containing all the mentioned covariates (called Model 1). Model 2 was obtained via a backward stepwise procedure, using thresholds of $p=0.10$ for removing variables and $p=0.05$ for adding variables to the model. Model 3 was the Model 2 plus sex and race (selected for being universal confounders).

Since there were concerns about the potential mediation effect of HbF in the relationship between age at baseline and reaching MTD within one year, we performed a mediation analysis as well (26). Specifically, we performed a model-based causal mediation analysis

where age was the independent variable, MTD was the outcome and HbF was the mediator (27). We began with the mediation model (linear regression, outcome = HbF, predictor = age) and then the outcome model (log-Poisson robust regression, outcome = MTD, predictors = age and HbF). After that, we summarized these results into the average causal mediation effects (ACME) and the average direct effects (ADE), and with testing determined that they are significantly different from zero. We reproduced a new similar analysis, but added the rest of covariates as predictors, in both mediation and outcome models. Since the main predictor is continuous (age), we performed both analyses (without and with covariates) comparing sequentially different levels of age (from 0 against 1 to 7 against 8).

We extended the initial survival analysis by drawing Kaplan-Meier failure curves stratified by two groups (age < 8 years and age > 8 years), keeping the original observation period of follow up (up to 5.7 years, as we did with the first figure). Here, we performed a Log-Rank test for comparing both survival curves. The cut point of 8 years was established after a sequential revision of different cut points (one by one, from 1 to 17). We stratified age by the first proposed cut point; we ran a Log-Rank test and saw its p value. We repeated this with all cut points (from 2 to 17 years of age). The cut point with the smallest p value was selected; it corresponded to a HU start age of 8 years.

We defined $p < 0.05$ as significant, performed confidence intervals at 95% (CI 95%) using robust standard errors and provided Wald test results for all estimated parameters. We used Stata v14.2 (StataCorp, Special Edition, College Station, Texas 77845 USA) and R v3.3.3 (only for the mediation analysis) as our analysis software.

3. Results

A total of 210 patients were included in the data analysis, with 48% of the subjects being male and 92% African American. The mean age at HU start was 6.6 years (standard deviation 4.8) and 22/210 (10%) started HU at greater than 13 years old. Table 1 shows the general distribution of the children's demographic and hematologic characteristics (for the complete sample of 210), stratified by reaching MTD within one year ($n=116$) or not ($n=94$). Two results from this table merit special attention: mean of age at baseline ($p=0.02$), which is higher in the second group ($n=94$); and HbF at baseline ($p=0.02$), which is higher in the first group ($n=116$). In total, 116 of the 210 patients analyzed (55%) reached MTD in less than 1 year, 56 (27%) patients reached MTD in greater than 1 year, and 38 (18%) patients had not yet reached MTD as of December 31, 2016. Figure 1a, a Kaplan-Meier failure curve for event (reaching MTD) versus time since HU initiation (in years), displays the raw data for time to MTD and shows an inflection point at one year. As previously mentioned, per (blinded) guidelines the starting dose of HU was 20 mg/kg/day. While the highest HU dose allowed by our guidelines was 35 mg/kg/day, the average MTD dose for the cohort was lower, at 25.5 mg/kg/day.

Table 2 shows a relationship between age at baseline and the outcome, which is visible in the crude estimate and two of three adjusted estimates. Statistically, the best model is Model 2, which has the smallest AIC (370.99). For this model, an adjusted $RR=0.97$ (95% CI 0.94–0.99; $p=0.02$) explains that per every one year of increase in age at baseline (i.e. age at HU

initiation) the chance of reaching MTD within one year decreases by 3% (on average). This estimate is still the same after controlling for confounders (see Model 3).

As seen in prior literature, HbF at baseline and age at baseline showed a strong inverse association ($\beta=-0.79$, CI95%:-0.95 to -0.64, $p<0.001$). The model-based causal mediation analysis showed there is not any mediation effect of HbF in the relationship between age at baseline and reaching MTD up to one year of follow up. After performing all the mediation and outcome models, with and without covariates, and checking them sequentially for different ages (from 0 against 1 to 7 against 8 in years); all the p values were >0.05 for all the indicators of interest: ACME, ACME average, ADE and ADE average.

Figure 1b provides the best age cut-point (8 years) for showing the evolution of reaching MTD before and beyond the threshold of one year. As seen in the figure, children aged 8-years or less at initiation of HU therapy are more likely to reach MTD in a year as compared to the older cohort (Log-rank test: $X(2)=4.4$; $p=0.04$). However, 85% (115/136) of the less than 8-year age cohort and 79% (57/74) of the greater than 8-year age cohort reached MTD within the entire follow up period. As such, in our cohort, age did not affect the overall likelihood of reaching MTD.

4. Discussion

Hydroxyurea (HU) has well-proven hematologic and clinical benefits, especially when escalated to the maximum tolerated dose (MTD). The results of this study show that even in a large academic institution, which often have resources for optimizing patient care unavailable in other settings such as social workers, care managers and other support staff, only 55% of the 210 patients analyzed reached MTD in less than one year. Our results support the idea that one year after HU treatment initiation is a critical point in the evolution of patients in terms of reaching MTD (Figure 1a). In this scenario, age at HU initiation plays a central role in that: a) the older a child starts his/her treatment, the lower their chances of reaching MTD within one year of HU treatment initiation; b) children aged 8 years or younger have a greater chance of reaching MTD within one year of HU treatment initiation. In other words, younger children are more likely to reach MTD within one year as compared to older children.

Due to the potential toxicities of administering HU, a myelosuppressive agent, researchers and clinicians have historically been cautious to administer this therapy to children and especially young children and infants. Indeed, the first trials excluded pediatric patients (21,28). However, as the clinical benefits and safety profile of HU became evident in adults, HU therapy was expanded to include children, with pediatric data showing HU to be very well tolerated (4). If present, side effects tend to be mild, with pain, headaches, abdominal discomfort, and nausea most commonly reported (14). Growth, development, and sexual maturation do not appear to be adversely affected (14,17,28,29). Given that a decrease in ANC is a known, predictable, and desired “toxicity” of HU-therapy and the baseline immunosuppressed state of patients with SCD, infection risk has been a valid concern. However, all published literature suggests there is not an increased risk of infection (4,11,16,30).

Data among very young children and infants have been equally reassuring. The HUSOFT trial, which enrolled young children from ages 6 to 28 months, and the subsequent extension study both showed that HU was tolerated well, with no increase rate in severe toxic events and sepsis rates comparable with previous controls (11,15). Further, BABY HUG, a randomized controlled trial of HU in children aged 9–18 months was published in the Lancet in 2011, concluding that “on the basis of safety and efficacy data, HU can now be considered for all very young children with sickle-cell anemia.” (8) For these reasons, current guidelines recommend offering HU therapy to all children with SCD starting at 9 months, regardless of symptoms or clinical status (22).

The safety and efficacy data previously published on HU therapy in very young children in conjunction with the present finding that children of younger age are more likely to reach MTD in a year suggests that every effort should be made to start HU therapy in very young children. One potential reason young children were more likely to reach MTD is adherence; in SCD and in other chronic diseases such as diabetes (31), cancer (32), and HIV (33), older children and adolescents are more likely to be non-adherent with their medications, and adherence is the often-cited barrier to proper HU therapy (34). An advantage of the current data is that it comes from outside the confines of a clinical trial, in which study participants are often monitored and followed up more closely than typical clinical practice. Published data has indeed shown that escalation to MTD often occurs more rapidly in these trials than found in our study. For example, the following trials, SWITCH (90% reached, with a mean of 32 weeks to reaching MTD (35)), HUG-KIDS (81%, mean 224 days (14)), and TWITCH (95%, based on laboratory parameters, mean appeared to be 40 weeks (36)), all had mean escalation times of less than one year. As such, the adherence and resultant consequences of the current study are more applicable to a typical clinical setting.

In such a setting, there are often delays in initiating or escalating HU. While not specifically analyzed in this study, potential causes of delay in reaching MTD include: 1) difficulties in developing a routine that incorporates daily administration, 2) missed appointments, and, 3) especially in young children, delays in dose escalation from myelosuppression secondary to viral illnesses. Further, not every child’s MTD is 35 mg/kg/day; for our cohort the average MTD dose was 25.5 mg/kg. This dose is similar to MTD doses in previously published trials, including Sustained MTD (MTD dose 25.9 mg/kg) (17), TCD Reduction (27.9) (37), Toddler HUG (28.0) (7), HUSTLE (25.1) (19), and SWITCH (25.4) (35). This inter-patient variability is another reason we chose to use time to MTD as a dichotomous rather than continuous variable, as differences in HU MTD dose are likely to be multi-factorial, involving genetic variation (38,39) and beyond the scope of this study. Given these real-world challenges, we believe that reaching MTD within the inflection point of one year is a reasonable and achievable goal.

Beyond starting HU at a young age, the data presented suggest that additional inventions to optimize HU therapy should be targeted to older children and children who take greater than one year to reach MTD. Reminders sent via text message approximately double medication adherence in other chronic diseases (40); similar interventions have been beneficial for HU therapy adherence in patients with SCD and could be areas of targeting intervention, especially older children with smart phones or those taking a daily medicine for the first

time (41). Incorrect dosing and fear of side effects of medication are two reported barriers to proper medication among pediatric patients with SCD (42); thus additional education on these topics specifically targeted at older patients or patients not yet at MTD after one year of HU therapy could improve outcomes.

Other studies have found parents to be hesitant towards HU given potential side effects, fear of cancer, not wanting to participate in required laboratory monitoring and follow up, or concern that HU will not be efficacious (43); these potential confounders have been previously reported and thus were not examined in the present study. Additionally, provider-level variability and barriers are important aspects that can impact medication prescribing habits and overall adherence, though not analyzed in the current study, as the practice since 2011 of the (blinded) Center has been to encourage HU therapy at MTD for all patients. Despite this encouragement, HU compliance may have been poor among some patients, and we did not employ a specific measure of quantifying HU compliance (such as pill counting or prescription monitoring), which represents a limitation to the study. Importantly, as a retrospective analysis, associations, not causation, can be concluded. Caution should be applied when extrapolating the results to different patients and patient populations, especially those patients being cared for in settings with different resources than a large, urban, academic institution such as (blinded). Thus, while these results may be applicable to the current patient population, these findings may not necessarily be predictive or generalizable.

The time to MTD was provider rather than laboratory determined. Although it would have been simpler to use strict hematologic or HU-dosing parameters, the accuracy of the study would have been compromised for several reasons. First and most important, the goal of our analysis was to report the actual time it takes to reach the patient's specific MTD. While clinicians may rely on laboratory data, the decision whether to escalate HU dosing is ultimately the provider's (outside a protocol-based clinical trial). For example, children often undergo suppression of hematologic counts for reasons other than HU (e.g., viral suppression); using only laboratory criteria could misclassify these children as at MTD. Alternatively, although the (blinded) Center's practice guidelines define MTD as ANC $2.0-4.0 \times 10^3$ cells/microliter, ARC $70-200 \times 10^9$ cells/liter, and the maximum HU dose 35 mg/kg, there exists variability between providers. Thus, the decision to not use numeric cut-offs helps avoid penalizing patients who were at MTD per their provider despite not meeting strict laboratory criteria. As such, in clinical practice the time to MTD is not the time until reaching specific laboratory parameters but rather the time until the provider determines the patient is at MTD, which we have attempted to replicate in this analysis. Further, this specific data – time to MTD in clinical settings – is absent from published literature and therefore warrants attention.

Our data show that there is a subset of pediatric patients with SCD who do not reach MTD and many who fail to do so in one year. These results, in combination with the previously published safety and efficacy data, suggest that it may be beneficial to start young children on HU therapy to maximize chances of reaching MTD, thereby increasing HU benefits, and that older children should receive additional therapy and interventions to reach MTD within

one year. Those patients who don't reach MTD within one year may need the most extensive intervention.

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Figure 1.

Figure 1a – None

Figure 1b - (blue line) Age <= 8 years (n=136/210);

(red line) Age > 8 years (n=74/210)

Table 1

Characteristics of the children at baseline

Characteristic	Mean (sd) or n[%]			p **
	Overall (n=210)	MTD reached within 1 year (n=116)	MTD not reached within 1 year* (n=94)	
Sex				
Male	101 [48.1]	54 [46.6]	47 [50.0]	0.68
Female	109 [51.9]	62 [53.5]	47 [50.0]	
Age (years)	6.6 (4.8)	5.8 (4.6)	7.4 (5.0)	0.02
Race				
Non-African American	16 [7.6]	7 [6.0]	9 [9.6]	0.44
African-American	194 [92.4]	109 [94.0]	85 [90.4]	
BMI (kg/m)	16.9 (3.1)	16.9 (3.4)	16.9 (2.8)	0.93
Hemoglobin Type				
Hemoglobin SS	200 [95.2]	109 [94.0]	91 [96.8]	0.52
Hemoglobin S Betathal	10 [4.8]	7 [6.0]	3 [3.2]	
Hemoglobin (g/dL)	8.1 (1.1)	8.2 (1.1)	8.1 (1.1)	0.76
Hemoglobin S %	78.1 (13.5)	78.2 (12.4)	78.0 (14.8)	0.91
Hemoglobin F %	13.2 (7.3)	14.2 (7.1)	11.9 (7.4)	0.02
White Blood Cell Count	13.3 (5.0)	13.2 (5.2)	13.5 (4.6)	0.67
Absolute Neutrophil Count	5.7 (3.6)	5.5 (3.4)	6.0 (3.7)	0.26
Absolute Reticulocyte Count	0.36 (0.14)	0.35 (0.15)	0.36 (0.13)	0.60

Table 1 shows the baseline (i.e. prior to HU initiation) characteristics for the study participants, for the whole sample and also sub-divided by MTD status

Bold – statistically significant (p<0.05)

* Not reached until the finish of the first 1 year observation period; however, some of these cases reached MTD after 1 year.

** ANOVA Oneway for continuous variables and Fisher's Exact for dichotomic variables

MTD is maximum tolerated dose. BMI is body mass index. Income is the median family income. WBC, ANC – 10^3 cells/microliter. ARC – 10^6 cells/microliter.

There is not missing data in this sample (n=210)

Table 2

Association between baseline sociodemographic and hematologic factors and reaching MTD within 1 year in the OVERALL sample (n=210)

Covariate	Crude			Adjusted		
	RR	(CI 95%)	p *	Model 1 RR	(CI 95%)	p *
Sex						
Male	ref	ref	ref	ref	ref	ref
Female	1.1	(0.83–1.4)	0.62	1.0	(0.82–1.4)	0.71
Age at baseline	0.97	(0.94–0.99)	0.02	0.97	(0.93–1.0)	0.10
Race						
Non-African American	ref	ref	ref	ref	ref	ref
African-American	1.3	(0.73–2.3)	0.39	1.3	(0.73–2.3)	0.37
BMI at baseline	1.00	(0.96–1.0)	0.93	1.0	(0.99–1.1)	0.23
Hemoglobin Type						
Hemoglobin SS	ref	ref	ref	ref	ref	ref
Hemoglobin S Betathal	1.3	(0.84–2.0)	0.25	1.3	(0.78–2.0)	0.35
Hemoglobin	1.0	(0.91–1.1)	0.76	0.97	(0.85–1.1)	0.71
Hemoglobin S	1.0	(1.0–1.0)	0.91	1.0	(1.0–1.0)	0.50
Hemoglobin F	1.02	(1.0–1.0)	0.02	1.0	(1.0–1.0)	0.28
White Blood Cell Count	0.99	(0.97–1.0)	0.68	1.0	(0.96–1.0)	0.87
Absolute Neutrophil Count	0.98	(0.94–1.0)	0.34	1.0	(0.94–1.1)	0.91
Absolute Reticulocyte Count	0.79	(0.33–1.9)	0.60	0.79	(0.28–2.3)	0.67
AIC **	-	-	-	390.30	370.99	376.14

* Wald test;

** For null model the AIC is 371.70; **Bold** – statistically significant (p<0.05)

Model 1 is the full model which includes all the variables listed in the first column. Model 2 is the one obtained by the stepwise procedure described in method section, including -in this case - just one variable: age at baseline. Model 3 is the model 2 plus sex, ethnicity and income. Robust variance was used for estimating standard errors. CI 95% is confidence interval at 95%.

Baseline is defined by the initiation of Hydroxyurea (HU) treatment. MTD is maximum tolerated dose and the outcome is reaching MTD within 1 year. MTD is maximum tolerated dose. BMI is body mass index. Income is the median family income. WBC, ANC – 10^3 cells/microliter. ARC – 10^6 cells/microliter.

There is not missing data in this sample (n=210)