ELSEVIER

Blood 142 (2023) 17–18

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Clinical and Hematopoietic Profiles Associated with Sustained Hydroxyurea Response for Patients with Sickle Cell Disease

Luisanna M Sanchez Ventura, MD[1], *Ijele Adimora, MD MBA*[2], *Emani C. Elliot*[1], *Titilope Fasipe, MD PhD*[1], *Jonathan M. Flanagan, PhD*[1]

[1] Texas Children's Cancer & Hematology Center, Baylor College of Medicine, Houston, TX
[2] The Johns Hopkins University School of Medicine, Baltimore, MD

Background: Hydroxyurea improves the lives of patients with sickle cell disease (SCD) by inducing expression of fetal hemoglobin (HbF). Higher HbF levels are associated with improved clinical outcomes. However, there is significant heterogeneity in long-term response to the drug. The impact of quantitative changes in hematopoietic stem and progenitor cells (HSPCs) during hydroxyurea treatment remains poorly characterized.
Objectives: (1) Determine the prevalence and clinical impact of declining hydroxyurea response in pediatric patients with SCD; and (2) Characterize HSPC profiles associated with hydroxyurea response.
Methods: We conducted a retrospective review of longitudinal clinical data from 760 pediatric patients with SCD seen at Texas Children's Hematology Center between 2010-2021. We selected patients consistently on hydroxyurea for >5 years for this study. We classified each subject according to their individual HbF response to hydroxyurea into: 1) *Sustained-Response* if the patient maintained an absolute HbF level >20% or 2) *Decreased-Response* if a patient's HbF levels decreased to <10% over time despite medication compliance. We obtained clinical and laboratory hydroxyurea treatment information for each individual. We isolated peripheral blood mononuclear cells (PBMCs) from whole blood collected from these patients during outpatient appointments. Patients were on a stable hydroxyurea dose without recent blood transfusions prior to collection. Flow cytometry was used to quantify the frequencies of ten HSPC populations in the PBMC samples.
Results: In total, 208 children with HbSS or HbSβ^0-Thalassemia were included in our analysis: 148 individuals (71%) had a *Sustained Response* and 60 (29%) experienced a *Decreased Response* to hydroxyurea. Subjects with a *Decreased Response* had a median initial hydroxyurea induced HbF of 23.9% that decreased to 9.8% over time compared to stable values of HbF >20% in the HU-Sustained Response group (p<0.001). These differences were consistent after adjusting for age (*Figure 1*). We found that patients who developed a *Decreased Response* to hydroxyurea experienced a significantly higher incidence of clinical complications, including number of visits to the emergency department (153.3 vs. 120.3 events per 100 patient-years), number of transfusions (37.4 vs. 11.9), and SCD-related hospitalizations (57.7 vs. 42.0). The causes of SCD-related hospitalizations included vaso-occlusive events requiring admission (27.7 vs 21.1 events per 100 patient-years), acute chest syndrome (13 vs 9.9), splenic sequestration (6.4 vs 3.5), and surgical procedures (7.47 vs 3.02). We also profiled HSPCs by flow cytometry using PBMCs collected from a subset of 40 patients (20 *Sustained Response* individuals vs. 20 *Decreased Response*). Individuals with a *Sustained Response* had increased numbers of hematopoietic multipotent cells (51.75% vs. 43%), hematopoietic stem cells positive for CD49F $^{++}$ (20.5% vs. 13.55%), and CD235a $^{+}$/CD71 $^{+}$ cells (11.55% vs. 4.54%). In contrast, individuals with a *Decreased Response* had an increased percentage of unipotent hematopoietic progenitor cells (38.55% vs. 52.9%) and committed megakaryocyte erythroid progenitor cells (33.2% vs 46.2%; *Figure 2*).
Conclusions: Nearly 30% of children with SCD taking hydroxyurea had a significant decline in their HbF levels after years of treatment and consequently suffered an increased number of clinical complications. While higher dosages of hydroxyurea may restore some HbF induction in these patients, we have quantified broad changes in specific HSPC levels that may be responsible for this decline in HbF. Patients with a *Decreased Response* had a lower percentage of multipotent progenitor cells that maintain self-regeneration capacity and increase numbers of committed erythroid progenitor cells. Although many stressors can impact quantitative and functional changes seen in HSPCs, these findings suggest that premature aging of the hematopoietic system plays an important role in long-term hydroxyurea response. Better understanding of why certain individuals are more susceptible to this phenomenon would enable the development of personalized strategies to enhance HbF induction and facilitate early selection of alternative treatments for these individuals with SCD.

Disclosures Fasipe: *Global Blood Therapeutics:* Consultancy, Ended employment in the past 24 months; *Forma Therapeutics:* Consultancy, Ended employment in the past 24 months; *Novartis:* Consultancy, Ended employment in the past 24 months.

Figure 1. Changes in fetal hemoglobin levels in age-matched patients from year 1 to year 10 of hydroxyurea treatment.

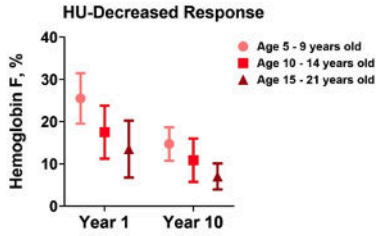

Figure 2. Difference in subsets of HSPCs collected from the peripheral blood of pediatric patients with SCD. Patients with *a Sustained Response* (white), have an overall increased proportion of hematopoietic multipotent cells, mainly driven by hematopoietic stem cells that are positive for $CD49F^{++}$ and $CD235a^{+}/CD71^{+}$. Individuals with a *Decreased Response* (purple) had an increased concentration of unipotent hematopoietic progenitor cells and committed megakaryocyte erythroid progenitor cells. HSC: Hematopoietic stem cells. NS: not statistically significant.

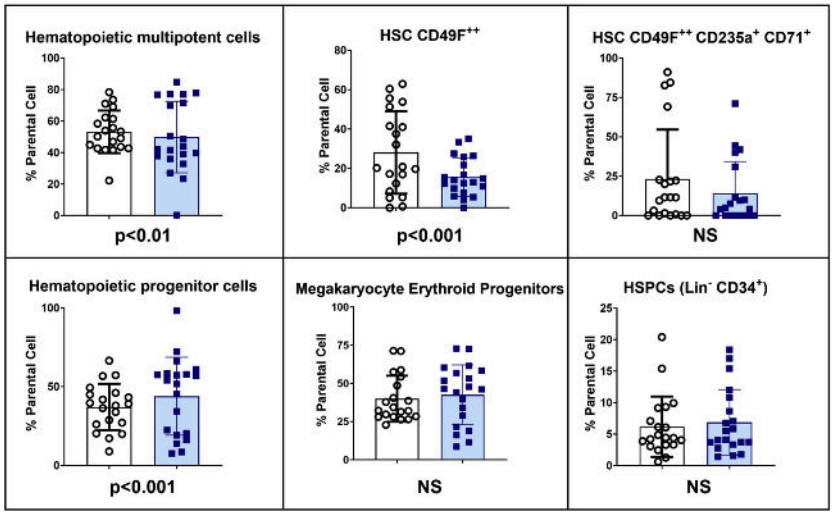

Figure 1

https://doi.org/10.1182/blood-2023-187335