Hydroxyurea Reduces the Transfusion Burden in Children with Sickle Cell Anemia: The Reach Experience

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Introduction: Many children with sickle cell anemia (SCA) require blood transfusions, which carry risks and utilize a scarce resource globally, particularly in Africa. Realizing Effectiveness Across Continents with Hydroxyurea (REACH, NCT01966731) has documented the safety, feasibility, and benefits of hydroxyurea for children with SCA living in sub-Saharan Africa. In REACH, hydroxyurea escalated to maximum tolerated dose (MTD) significantly decreased vaso-occlusive events, malaria, and death; transfusions were decreased by ~70% over 30 months of treatment when compared to the 2-month screening period. Characterizing and investigating how hydroxyurea reduces transfusion needs in REACH could contribute to improved clinical understanding and lead to better outcomes, a decreased transfusion burden, and preservation of the blood supply in these limited-resource settings.

Methods: Transfusions were recorded prospectively in the REACH REDCap electronic database. Using time-varying predictors and landmark analysis, transfusions during screening and treatment were analyzed by clinical site, calendar month, age, gender, splenomegaly, hydroxyurea dose, MTD status, baseline and latest laboratory values (Hemoglobin, MCV, HbF, absolute neutrophil count, and platelets, all measured at least 30 days prior to the transfusion), alpha thalassemia trait, and G6PD deficiency. Incidence rate ratios (IRR) were calculated for treatment periods compared to screening. Univariate relationships were assessed using the
Anderson-Gill model, plus multiple regression to estimate Hazard Ratios (HR) with 95% confidence intervals (CI’s).

Results: A total of 635 children with SCA enrolled in REACH, and 606 started hydroxyurea treatment. During screening, 48 transfusions were given to 43 children, and during the treatment phase 405 transfusions were administered to 214 children over an average treatment time of 5.2 ± 1.3 years. The transfusion rate was 43.3 per 100 patient-years during screening, which decreased to 22.0 per 100 patient-years during the initial fixed dose treatment period (IRR = 0.50; 95%CI = 0.35-0.74, p<0.001 compared to screening) and then decreased further to 12.1 per 100 patient-years during the dose escalation period (IRR = 0.28; 95%CI = 0.21-0.39, p<0.001 compared to screening; IRR = 0.54; 95%CI = 0.43-0.73, p<0.001 compared to fixed-dose). For every 100 children treated for a year with hydroxyurea during dose escalation, there were 31.4 fewer transfusions compared to the untreated screening period. Comparison of the indications for transfusion between the screening and treatment periods revealed transfusions administered for anemia decreased from a rate of 26.1 to 5.1 per 100 patient-years (p<0.001), while transfusions for malaria trended toward a decrease from 7.2 to 3.8 per 100 patient-years (p=0.08). Lower transfusion rates on hydroxyurea were associated with higher hemoglobin concentration (HR = 0.72 per 1g/dL increase; 95%CI = 0.65-0.78, p <0.0001) and higher HbF levels (HR = 0.80 per 10% increase, 95%CI = 0.69-0.92, p=0.0071). Those with palpable splenomegaly had higher transfusion rates (HR = 1.58, 95%CI = 1.22-2.03, p=0.0094). Age, gender, alpha thalassemia trait, G6PD deficiency, and neutrophil count were not associated with differences in transfusion rates.

Conclusion: Hydroxyurea significantly reduces blood transfusion administration in children with SCA in sub-Saharan Africa, especially when escalated to MTD. Transfusions for the sole indication of anemia decreased significantly on hydroxyurea treatment, likely due to higher treatment-associated hemoglobin levels and decreased hemolysis, and transfusions for malaria also trended toward a decrease. Splenomegaly remains a risk factor for transfusions despite hydroxyurea treatment. Overall, increased access to and implementation of hydroxyurea treatment for children with SCA across sub-Saharan Africa may not only improve individual patient outcomes through reduction in anemia, transfusion burden, and transfusion-associated complications including infections, but may also help preserve the scarce blood supply for the benefit of the larger population.
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