inside blood commentary

14 DECEMBER 2017 | VOLUME 130, NUMBER 24

CLINICAL TRIALS AND OBSERVATIONS

Comment on Opoka et al, page 2585

Hydroxyurea for SCA in Africa: no malaria harm

Isaac Odame THE HOSPITAL FOR SICK CHILDREN

In this issue of *Blood*, Opoka et al report no increased incidence of clinical malaria in a randomized trial of hydroxyurea therapy compared with placebo among young African children with sickle cell anemia (SCA).[1]

Sub-Saharan Africa shoulders the heaviest burden of SCA with more than 220 000 affected babies born in this region annually, less than half of whom survive beyond the age of 5 years.[2,3] In contrast, in high-income countries with low disease burden, more than 90% of affected children survive into adulthood as a result of a combination of interventions, including newborn screening programs and delivery of comprehensive care.[4] Disease-modifying therapies, including hydroxyurea, chronic blood transfusion, and hematopoietic stem cell transplantation, have proven efficacy in both children and adults in reducing SCA-related complications such as recurrent pain, acute chest syndrome, and stroke. Of these disease-modifying therapies, hydroxyurea could be the most affordable and feasible option in low-resource settings with limited clinical and laboratory infrastructure. Provided it is proven to be safe and to have the same predictable efficacy as in high-income countries, hydroxyurea treatment for children with SCA would be of the greatest benefit in sub-Saharan Africa.

What are the safety concerns for hydroxyurea treatment of children with SCA in sub-Saharan Africa? Malaria is endemic in this region (mostly *Plasmodium falciparum* malaria, the most severe form of the infection). The United Nations Children's Fund (UNICEF) has reported that in 2015, 80% of the more than 400 000 deaths from 214 million cases of clinical malaria worldwide occurred in children younger than 5 years old, mostly in sub-Saharan Africa.[5] Clinical studies have shown that although there is no increased risk of malaria in children with SCA in sub-Saharan Africa, mortality is still considerably higher in children with SCA who are hospitalized with malaria than in children without SCA.[6] In vitro and in vivo animal studies have generated contrasting data that support both potential risks and benefits for malaria infection in response to hydroxyurea treatment, but definitive human data are lacking.[7,8] Thus, the potential risk of an increase in malaria incidence and/or severity related to treatment with hydroxyurea poses a significant barrier to recommending its use in sub-Saharan Africa, the region that needs it most. In addition, hydroxyurea-induced neutropenia could cause increased severity of bacterial infections, which are common among African children with SCA.[9]

To address the aforementioned questions, Opoka et al designed NOHARM (Novel use Of Hydroxyurea in an African Region with Malaria) as a randomized, double-blind, placebo-controlled trial in Uganda, where malaria is endemic, comparing hydroxyurea at 20 mg/kg for 12 months with placebo. The primary outcome was incidence of clinical malaria. One may ask whether a placebo trial of hydroxyurea in children with SCA in sub-Saharan Africa is justified, given the weight of evidence in support of its efficacy in high-income countries. However, African expert clinicians and ethics board members viewed the research question as being of high importance, and they achieved consensus in approving the placebo-controlled study design, provided that study participants would have the opportunity to receive subsequent open-label hydroxyurea if no serious harms were observed from the blinded phase of the trial. NOHARM is the first randomized trial of hydroxyurea in sub-Saharan Africa.

The NOHARM trial results show that the 2 treatment arms did not differ in the incidence or severity of clinical malaria, incidence of clinical sepsis, number of laboratory adverse events, or dose-limiting toxicities including neutropenia. Also of note, the laboratory and clinical benefits were similar to those observed in previous US trials. The proportion of children with a composite outcome of 1 or more SCA-related clinical adverse events (vaso-occlusive pain crisis, dactylitis, acute chest syndrome/pneumonia, acute splenic sequestration, or blood transfusion) was significantly lower in the hydroxyurea arm than in the placebo arm. These data suggest that hydroxyurea at a fixed dose of 20 mg/kg is safe and efficacious, at least in the short-term, and should be strongly considered as an important disease-modifying treatment for young children with SCA in areas where malaria is endemic.

There are caveats to interpreting the results of NOHARM. The incidence of clinical malaria was very low in this study cohort compared with what has previously been reported in Ugandan children, most likely a reflection of the effective malaria prevention (insecticide-treated bed nets and monthly sulfadoxine-pyrimethamine) provided to all study participants. Since 2000, the worldwide

effort to combat malaria through the distribution of insecticide-treated bed nets and chemoprophylaxis has resulted in a 65% reduction in malaria-related mortality.[5] The 2010 World Health Organization African Regional Strategy recommends that children with SCA in sub-Saharan Africa receive some form of malaria prevention.[10] But bed net coverage in Africa still remains patchy, and whether or not chemoprophylaxis should occur and which specific chemoprophylaxis to use are not well established. Thus, the findings of NOHARM may not apply to children with SCA who do not receive malaria chemoprophylaxis or use insecticide-treated bed nets.

The duration of treatment with hydroxyurea was only 12 months and thus provided no information about the longer-term effects of hydroxyurea treatment in children with SCA in sub-Saharan Africa. The extended open-label phase of hydroxyurea therapy in this cohort will help generate longer-term data to guide implementation of hydroxyurea therapy in these settings. The study participants were seen for scheduled visits once per month for the first 4 months, then once every 2 months for the next 8 months, a total of 10 scheduled visits per year including the randomization visit and 2 weeks after treatment initiation. Would this frequency of clinic visits by patients and families be feasible as a standard of care in sub-Saharan Africa?

With the reassuring results of NOHARM regarding safety of hydroxyurea treatment, placebo-controlled trials in sub-Saharan Africa would no longer be justified. Rather, open-label studies with longer follow-up to explore different dosing schemes that allow for less frequent and rigorous laboratory monitoring should be conducted. Dose-limiting toxicities were low at the 20 mg/kg fixed dose of hydroxyurea in the NOHARM trial, suggesting that less frequent monitoring would be more feasible and safer with this dosing regimen compared with dose escalation to the maximum tolerated dose.

The results of the NOHARM trial help address a major barrier to using hydroxyurea treatment in children with SCA in regions where malaria is endemic, thereby moving clinicians a step closer to its wider use across sub-Saharan Africa.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Opoka RO, Ndugwa CM, Latham TS, et al. Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a trial for children with sickle cell anemia. *Blood*. 2017;130(24):2585-2593.
2. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun*. 2010; 1(8):104-111.
3. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. *Am J Prev Med*. 2011; 41(6 suppl 4):S398-S405.
4. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. *Blood*. 2010;115(17):3447-3452.
5. UNICEF. Malaria mortality among children under five is concentrated in sub-Saharan Africa. Updated February 2017. http://data.unicef.org/topic/child-health/malaria/#.
6. McAuley CF, Webb C, Makani J, et al. High mortality from *Plasmodium falciparum* malaria in children living with sickle cell anemia on the coast of Kenya. *Blood*. 2010;116(10):1663-1668.
7. Brun M, Bourdoulous S, Couraud PO, Elion J, Krishnamoorthy R, Lapoumeroulie C. Hydroxyurea downregulates endothelin-1 gene expression and upregulates ICAM-1 gene expression in cultured human endothelial cells. *Pharmacogenomics J*. 2003;3(4):215-226.
8. Cabrales P, Zanini GM, Meays D, Frangos JA, Carvalho LJ. Nitric oxide protection against murine cerebral malaria is associated with improved cerebral microcirculatory physiology. *J Infect Dis*. 2011;203(10):1454-1463.
9. Ramakrishnan M, Moïsi JC, Klugman KP, et al. Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(5):329-337.
10. World Health Organization Regional Office for Africa. Sickle cell disease: a strategy for the WHO African region. http://www.who.int/iris/handle/10665/1682.

DOI 10.1182/blood-2017-10-812974

● ● ● LYMPHOID NEOPLASIA

Comment on Mar et al, page 2631

SETD2: a complex role in blood malignancy

Jonathan D. Licht UNIVERSITY OF FLORIDA HEALTH CANCER CENTER

In this issue of *Blood*, Mar et al describe the effect of inactivating mutations of the histone methyltransferase (HMT) SETD2 in accelerating leukemia pathogenesis and conferring therapy resistance.[1] Mutations of epigenetic regulators are among the commonest lesions in malignancy. These include mutations of HMTs that modify histone tails protruding from the nucleosome. For example, inactivation of EZH2, responsible for histone H3 lysine 27 trimethylation (H3K27me3), a modification associated with gene silencing, occurs in myelodysplasia and acute myeloid leukemia (AML), whereas mutation of KMT2D, responsible for the H3K4me1 modification found at enhancers, is common in lymphoma. These enzymes change the chemical composition of chromatin at gene regulatory sites, affecting transcriptional initiation. By contrast, SETD2 has a role downstream of the transcriptional start site (TSS).

Mutations of *SETD2*, including truncating mutations, are commonest in clear cell renal carcinoma (~20%) and are found in 5% to 10% of cases of a wide variety of tumors, including melanoma, bladder, lung, and uterine (www.cbioportal.org). *SETD2* mutations were found in 12% of cases of B-cell acute lymphoblastic leukemia, 1% to 2% of cases of B-cell lymphoma, chronic lymphocytic leukemia, and AML, and occasionally cases of myeloproliferative neoplasm. SETD2 is the sole mammalian HMT that catalyzes H3K36 trimethylation (H3K36me3). SETD2 associates with elongating RNA polymerase, creating H3K36me3-modified nucleosomes 3′ to the TSS that serve as docking sites for the FACT histone chaperone and assembly complex. Thus, H3K36me3 methylation by SETD2 and recruitment of tight arrays of nucleosomes prevent the spurious reinitiation of transcription within gene bodies. H3K36me3 also recruits DNMT3B, leading to the dense methylation of gene bodies, which reinforces intragenic silencing.[2] In addition, H3K36me3 helps direct the splicing machinery to intron/exon boundaries.