Background: Hydroxyurea has proven safety, feasibility, and efficacy in children with sickle cell anemia in sub-Saharan Africa, with studies showing a reduced incidence of vaso-occlusive events and reduced mortality. Dosing standards remain undetermined, however, and whether escalation to the maximum tolerated dose confers clinical benefits that outweigh treatment-related toxic effects is unknown.

Methods: In a randomized, double-blind trial, hydroxyurea at a fixed dose (approximately 20 mg per kilogram of body weight per day) was compared with dose escalation (approximately 30 mg per kilogram per day). The primary outcome was a hemoglobin level of ⩾9.0 g/dL or a fetal hemoglobin(HbF) level of ⩾ 20% after 24 months. Secondary outcomes included the incidences of malaria, vaso-occlusive crises, and serious adverse events.

ACADEMIC P.E.A.R.L.S

Pediatric Evidence And Research Learning Snippet

Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa.

Chandy C. John, Robert O. Opoka et al. N Engl J Med 2020;382:2524-33. DOI: 10.1056/NEJMoa2000146

RESULTS:
Children received hydroxyurea at a fixed dose (94 children; mean [±SD] age, 4.6±1.0 years) or with dose escalation (93 children; mean age, 4.8±0.9 years); the mean doses were 19.2±1.8 mg per kilogram per day and 29.5±3.6 mg per kilogram per day, respectively.
At trial closure, 86% of the children in the dose-escalation group had reached the primary-outcome thresholds, as compared with 37% of the children in the fixed-dose group (P<0.001). Children in the dose-escalation group had fewer sickle cell–related adverse events (incidence rate ratio, 0.43; 95% confidence interval [CI], 0.34 to 0.54), vaso-occlusive pain crises (incidence rate ratio, 0.43; 95% CI, 0.34 to 0.56), cases of acute chest syndrome or pneumonia (incidence rate ratio, 0.27; 95% CI, 0.11 to 0.56), transfusions (incidence rate ratio, 0.30; 95% CI, 0.20 to 0.43), and hospitalizations (incidence rate ratio, 0.21; 95% CI, 0.13 to 0.34). Dose-limiting toxic effects were similar in the two groups, and there were no cases of severe neutropenia or thrombocytopenia.

Conclusion: Hydroxyurea with dose escalation had superior clinical efficacy to that of fixed-dose hydroxyurea, with equivalent safety

Key Message: Hydroxyurea is safe in sickle cell anemia patients and an attempt to increase the dose to up to 30mg/kg/day should be considered using a target of mild myelosuppression (absolute neutrophil count, 2.0×109 to 4.0×109 per liter), which is unlikely to cause severe cytopenia or clinical toxic effects so as to reduce the sickle cell induced events

EXPERT COMMENT

"Hydroxyurea in sickle cell anemia has been a game changer. The worry of initiation of hydroxyurea due to fear of severe neutropenia and thrombocytopenia has been a concern for a long time. This is the first study which has shown in a systematic randomized study that there is acceptable level of toxicity with introduction of hydroxyurea at higher doses of up to 30mg/kg/day using a surrogate marker of mild myelosuppression (absolute neutrophil count, 2.0×109 - 4.0×109 per liter). The higher doses also reduce the number of events due to sickle cell thereby reducing the financial burden by decreasing hospital stay, requirement of blood transfusion and supportive care."

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Reference

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