Hydroxyurea in Sickle Cell Disease

Background:

Pain is the most common symptom of SCD. Adults with SCD report pain half of all days, but seek care only 3.5% of those days. Pulmonary complications are also common in SCD and acute chest syndrome (ACS) is the leading cause of acute death. Many factors affect the severity of an individual's experience with SCD, but the most established variable is fetal hemoglobin level, with high levels being protective against pain and ACS.

Hydroxyurea has been used since the 1950s in myeloproliferative diseases. It is known to increase Hgb F levels, is therapeutic with once daily dosing, and highly bioavailable. Two large, multicenter, well planned studies demonstrated that Hydroxyurea is well tolerated and increased Hgb F in the majority of sickle cell patients. Three large randomized trials have been done since, as well as 51 smaller observational studies, 33 of which included children. In addition to increasing Hgb F, Hydroxyurea decreases circulating leukocytes, platelets, and reticulocytes, alters expression of adhesion molecules, and improves deformability and rheology of RBCs.

Results of Studies in Adults:

Lower annual rates of pain crises (2.5 per yr v 4.5 per yr)
Lower incidence of ACS (50%)
Reduced need for blood transfusions
Lower cost for hospitalizations

Children: BabyHug, HUG KIDS

Equivocal for organ function, but increased Hgb level, increased Hgb F, decreased pain, decreased ACS, no neurotoxicity or impact on growth and only toxicity is reversible cytopenias. Possible neuroprotection with fewer abnormal TCDs.

Few studies in Hgb S B+ Thal or Hgb SC disease

Recommendations for use in sickle cell anemia:

1) Use a treatment protocol to ensure adequate dosing and monitoring
2) Educate **all** patients and families about Hydroxyurea
3) Treat all with 3 or more moderate to severe pain episodes in past 12 months
4) Treat all with chronic pain
5) Treat all with severe or recurrent ACS
6) Treat all with severe symptomatic chronic anemia
7) Infants 9 months or greater, *offer* treatment regardless of clinical severity to reduced SCD related complications
8) Use in all with chronic kidney disease
9) Consider use in those with Hgb S Beta+ Thalassemia or Hgb SC with frequent pain
10) Discontinue for pregnant or breastfeeding

Treatment and Monitoring:

1) At initiation: CBC with retic, CMP, Hgb F, pregnancy test (counsel for contraception)
2) Start 15 mg/kg/day in adults (round up to nearest capsule); start 5-10 mg/kg/day in CKD
   Start 20 mg/kg/day in infants and children
3) Monitor CBC with differential and retic every 4-6 weeks when adjusting dose
4) Aim for target ANC > 2000 (down to 1250 in children), platelets > 80,000. If lower, hold dose and check counts weekly, re-initiate at 5 mg/kg/day lower than last dose
5) Increase dose by 5 mg/kg/day every 6-8 weeks until myelosuppression, other toxicity, or 35 mg/kg/day
6) Once at stable dose, check CBC and retic every 2-3 months
7) 6 month minimal trial period on maximum tolerated dose is recommended