Hydroxurea: A Novel Approach to Optimizing the Health of Pediatric Patients with Sickle Cell Disease

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Outline

• Sickle Cell Disease
  – Pathophysiology and Clinical Manifestations
• What is hydroxyurea?
  – Mechanism of action
• Clinical Benefits
• Landmark Studies
  – MSH Hydroxyurea Trials
  – Baby Hug
  – SWITCH
  – TWITCH
• Recommendations
Pathophysiology

Common Clinical Complications of Sickle Cell Disease.

Common Clinical Complications of Sickle Cell Disease.

Hydroxyurea in SCD

- HbF critical predictor of sickle cell disease

- Pharmacologic induction of HbF is a key goal in the treatment of SCD

Hydroxyurea – Mechanisms of action

Multiple beneficial effects

1. **HbF induction in erythroid precursors**
2. Lower neutrophil and reticulocyte counts
3. Decreased adhesiveness & reduced rheology of RBCs and neutrophils
4. Decreased hemolysis – macrocytosis, hydration, dec. sickling
5. NO release with potential local vasodilation & improved vascular response

Russell E. Ware Blood 2010;115:5300-5311
Clinical Benefits of Hydroxyurea

• Improved
  – Hemoglobin
  – Hemoglobin F
  – QOL
  – Survival

• Decreased
  – Pain
  – Hospitalization
  – Acute chest syndrome
  – Need for transfusions

• Clinically equivalent to PRBC transfusions in preventing stroke in patients with elevated TCD
Laboratory and morphologic changes during hydroxyurea dose escalation to MTD

Russell E. Ware Blood 2010;115:5300-5311

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Time line of hydroxyurea therapy for SCA

>30 years clinical experience with hydroxyurea for patients with sickle cell anemia

Russell E. Ware Blood 2010;115:5300-5311
Effect of Hydroxyurea on Painful Crises

- Multicenter, double blinded, RCT to assess hydroxyurea efficacy in adults
- 299 patients, 152 on hydrea arm
- Effects
  - ↓Pain, ACS, need for transfusions
  - Lower costs for hospitalizations for pain
  - ↑Hb, HbF

Hydroxyurea in very young children with sickle cell disease
Baby Hug Study Results

- Multicenter, double blinded, RCT of 193 patients, 9-19 months
- Received hydroxyurea (20mg/kg) or placebo for 2 years
- Endpoints
  - $1^0$ - Splenic Function
  - $2^0$ – pain, dactylitis, ACS, Hb, HbF, etc

Hydroxyurea in very young children with sickle cell disease

Baby Hug Study Results

Hydroxyurea in very young children with sickle cell disease

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Hydroxyurea in very young children with sickle cell disease

Baby Hug Study Results

Wang et al. Lancet. 2011 May 14;377(9778):1663-72
Hydroxyurea in very young children with sickle cell disease

Baby Hug Study Results

Hydroxyurea for Primary Stroke Prevention

TWITCH Trial Results

• Phase III randomized, non-inferiority trial comparing standard therapy (transfusions) to alternate therapy (hydroxyurea) in children with abnormal TCD

• Excluded children with severe vasculopathy

• Randomized 121 patients
  – 61 to chronic transfusions (standard of care)
  – 60 to hydroxyurea

Ware RE, et al. Lancet. 2016 Feb 13;387(10019):661-70
Hydroxyurea for Primary Stroke Prevention

TWITCH Trial Results

- Results - HU is non-inferior to RBC transfusion in stroke prevention

Ware RE, et al. Lancet. 2016 Feb 13;387(10019):661-70
Hydroxyurea for Secondary Stroke Prevention

• SWITCH Trial
  – Phase 3, multicenter, non inferiority trial comparing the standard treatment for stroke (transfusion/chelation) to alternate treatment (hydroxyurea/phlebotomy)
  – Based on pilot data, efficacy of HU to reduce secondary stroke rates was not equivalent to transfusions.
  – “Acceptable” stroke margin would be offset by improved liver iron control through phlebotomy compared with chelation.
  – 134 patients underwent randomization
Event-free (Kaplan-Meier) plots of adjudicated neurologic events for the SWiTCH trial, by treatment group.

- 10% recurrent stroke risk (7 strokes) - all on HU arm
  - 1 fatal hemorrhagic stroke
- 20 TIAs among 15 patients
  - 9 standard treatment
  - 6 alternative treatment
- LIC was not significantly different b/n the 2 groups
## Clinical Effectiveness of Hydroxyurea
### CHOA Experience

<table>
<thead>
<tr>
<th></th>
<th>Rate Ratio</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Hospitalizations</td>
<td>0.53</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>(0.43 – 0.66)</td>
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<tr>
<td>Inpatient Days</td>
<td>0.50</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>(0.40 – 0.63)</td>
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<tr>
<td>ER visits</td>
<td>0.57</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>(0.49 – 0.67)</td>
<td></td>
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<tr>
<td>Pain encounters</td>
<td>0.64</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>(0.51 – 0.81)</td>
<td></td>
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<tr>
<td>Acute chest syndrome</td>
<td>0.57</td>
<td>0.0036</td>
</tr>
<tr>
<td></td>
<td>(0.39 – 0.83)</td>
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<tr>
<td>Blood Exposure</td>
<td>0.43</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>(0.29 – 0.64)</td>
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Probability of 10-year overall survival in sickle cell disease (SCD) patients who received hydroxyurea and in SCD patients who were conventionally treated: 86% versus 65% (P = .001).

Voskaridou et al. Blood 2010;115:2354-2363

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Survival among children and adults with sickle cell disease in Belgium: Benefit from hydroxyurea treatment

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Side Effects of Hydroxyurea

- Bone marrow suppression
  - Reversible cytopenia
- Reproductive effects
  - Low evidence, minimal human data exist about potential harmful reproductive effects of hydroxyurea in males and females
- Leukemia
  - No supporting evidence in SCD, over 2 decades of experience
- Others
  - Minimal published data to support causality
Hydroxyurea Treatment Recommendations for Children with Sickle Cell Anemia

For infants 9 months of age and older, children, & adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce sickle cell related complications

Evidence-Based guidelines for SCD: https://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines
How we manage pediatric patients with SCD on hydroxyurea

- Educate all families with sickle cell anemia about hydroxyurea & offer it to all patients with SCA at a year of age
- Baseline labs
  - CBC, Hb electrophoresis (HbF), CMP
- Start at 20mg/kg
- Monitor CBC q4wks for ~2-3 months, then every q8wks, once on stable dose
- Dose escalate by 5mg/kg q8weeks until maximum tolerated dose (target ANC ~ 2,000 – 4000)
- Monitor MCV and HbF levels for evidence of lab response and compliance.
Thank You

Questions?