Hydroxyurea revisited: the asymptomatic patient

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Outline

• The asymptomatic patient
• Natural history of sickle cell disease
• Hydroxyurea: where are we?
• Indication for hydroxyurea therapy
• How we treat
• Conclusion
The perception of an “asymptomatic” sickle cell disease is a misnomer.
Outcome of sickle cell anemia: A 4-decade observational study of 1056 patients

• 73% had 1 or more clinically recognized forms of irreversible organ damage.

• By the fifth decade, 48% had documented irreversible organ damage.
  – ESRD 11.6%
  – Sickle cell chronic lung disease 16% (often associated with pulmonary hypertension)
  – Cerebrovascular accident 11%

Case 1

• African girl from Burundi with Hb SS disease. Initially seen at age 7 mths, asymptomatic, lost to follow-up, reappeared in our clinic 11/08, no pain issues or complications. Noted to be quiet and downcast, not active, but parents report that she does play and talk at home.

• At 3 yrs of age, TCD wnl, baseline Hgb F (15-20%), WBC 11k, Hgb > 9g/dl LDH 658, Tbili~2

• We introduced the concept of hydroxyurea, and at 5 yrs of age was started on hydroxyurea therapy.
Known facts

• Children with sickle cell disease (SCD) without overt symptoms have progressive, subclinical, age dependent chronic organ dysfunction
• No reliable predictive models for SCD severity
• Clinical care for affected individuals have been mainly supportive
• Survival gains mainly due to improved pediatric care and survival
## Progression of organ disease

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dysfunction</th>
<th>Author</th>
</tr>
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<tbody>
<tr>
<td><strong>Brain</strong></td>
<td>25% of children with HbSS have silent cerebral infarcts on surveillance MRI before age 6 years; by 14 years of age 37% have silent cerebral infarct</td>
<td>Kwiakowski et al. BJH 2009</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Of the 232 patients who died, 73% had 1 or more clinically recognized forms of irreversible organ damage. 77% of affected patients had sickle chronic lung disease.</td>
<td>Powars et al. 2005</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Increase in glomerular hyperfiltration begins in infancy, with progression to CKD in majority</td>
<td>Ware et al. BABY HUG trial, 2010</td>
</tr>
</tbody>
</table>
Mortality in SCD: CSSCD study

Patient survival

Patients ages ≥ 20yrs

- Hb SC pts survived longer
- SCA Life expectancy decreased by 25-30yrs
- Mortality highest amongst symptomatic patients
- 33% of death in pts without chronic organ failure mainly due to stroke, ACS and acute pain episodes.

Platt et al. NEJM, 1994; 330:1639-44
# Risk factors for early death in patients with SCA ≥ 20yrs: CSSCD

<table>
<thead>
<tr>
<th>Clinical and laboratory variables</th>
<th>Definition</th>
<th>Variable Estimate ± SE</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical factors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Seizures</td>
<td>Major or minor</td>
<td>0.91 ± 0.42</td>
<td>0.04</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>&gt;1 episode per year</td>
<td>0.80 ± 0.27</td>
<td>0.005</td>
</tr>
<tr>
<td>Renal failure</td>
<td>20% increase in crcl</td>
<td>1.10 ± 0.47</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Laboratory parameters</strong></td>
<td></td>
<td></td>
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<tr>
<td>HbF%</td>
<td>≤ 8.6%</td>
<td>- 0.09 ± 0.04</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WBC</td>
<td>&gt; 15,100 per cubic ml</td>
<td>0.10 ± 0.04</td>
<td>0.01</td>
</tr>
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</table>

*Multiple regression analysis

Platt et al. NEJM, 1994; 330:1639-44
What therapy can decrease the established risk factors for earlier death (decrease pain, ACS and WBC, increase Hb F)?
Hydroxyurea- mechanism of action

- A cytotoxic, antimetabolic and antineoplastic agent
- Potent inhibitor of ribonucleotide reductase
- Directly inhibits the RR M2 subunit
- An S-phase-specific agent, inhibits DNA synthesis and eventually cellular cytotoxicity
Clinical effects of hydroxyurea

Illustration courtesy of Alice Y. Chen
Peripheral blood smear morphology in sickle cell anemia and response to hydroxyurea therapy.
Multicenter study of hydroxyurea in adults with SCA: MSH trial

- Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia
  » Charache et al., NEJM 332:1317, 1995

- Methods: RCT of HU in Hb SS disease.
  – HU escalated to marrow suppression (maximum dose of 35 mg/kg)
  – 152 HU/147 placebo patients
  – Mean follow-up: 21 months
# Results of the MSH trial in SCA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hydroxyurea</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual pain episodes</td>
<td>2.5 episodes/yr</td>
<td>4.5 episodes/yr</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to 1st crisis</td>
<td>3.0 months</td>
<td>1.5 months</td>
<td>0.01</td>
</tr>
<tr>
<td>Median time to 2nd crisis</td>
<td>8.8 months</td>
<td>4.6 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute chest syndrome (rate per year)</td>
<td>25/152 patients (16.5%)</td>
<td>51 patients (35%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfusions</td>
<td>48 patients</td>
<td>73 patients</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin F%</td>
<td>75th percentile</td>
<td>25th percentile</td>
<td>NA</td>
</tr>
</tbody>
</table>

Charache et al., NEJM 332:1317, 1995
Impact of hydroxyurea on clinical events in the BABYHUG trial

- Infants with SCA (beginning at 9-18 months of age)
- Randomized to HU (20 mg/kg/d) or placebo
- n=193, 374 patient-years of on-study observation
- Hydroxyurea was associated with
  - lower rates of initial and recurrent episodes of pain, dactylitis, ACS and hospitalization
  - infants who were asymptomatic at enrollment had similar clinical benefit with hydroxyurea.
  - well tolerated, no increased toxicity

Thornburg et al. Blood. 2012;120(22):4304-4310
Given the risk factors for death and hydroxyurea’s impact on these risk factors, do we expect hydroxyurea to decrease rate of death?
Effect of hydroxyurea on mortality in adult sickle cell anemia in the MSH trial

- After 9 years of follow-up:
  - Mortality was associated with HbF concentration, rate of acute pain episodes and acute chest syndrome
  - Hydroxyurea was associated with a 40% reduction in mortality (P = 0.04)

- After 17.5 years of follow-up:
  - 43.1% of cohort died (4.4/100 person yrs)
  - 87.1% in patients who took no hydroxyurea

Steinberg et al., AJH 85: 403-408, 2010
Cumulative mortality from the MSH trial based on cumulative hydroxyurea exposure

P < 0.0001

Steinberg et al., AJH 85: 403-408, 2010
Effect of hydroxyurea on morbidity and mortality in SCD: results of a 17-year, single-center trial (LaSHS) Greece

Overall survival

Other outcomes

- Survival benefit was across all phenotypes (ages 16+)
- The HU group had reduction in the frequency of acute pain, transfusion requirements, hospital admissions, and incidence of ACS.
- Baseline HbF and change in LDH were predictive of OS

The effect of hydroxcarbamide therapy on survival of children with sickle cell disease: Brazilian cohort

Overall survival for all pts

Other outcomes

• Ages 3-18 years with SCD met disease severity criteria.
• Median dose of 20.8 mg/kg/d
• Compared to untreated pts, those on HU had improved lab indices, less severity, and overall survival (p=0.01).

Lobo et al., BJH. 2013 Jun;161(6):852-602013,
## Meta analysis of adult trials on effect of hydroxyurea on mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Number on and not on HU</th>
<th>Median follow up in years on and off HU or patient years</th>
<th>Death rate off HU</th>
<th>Death rate on HU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobo et al. (table 4) *</td>
<td>293/1045</td>
<td>0.59 per 100</td>
<td>0.08</td>
<td></td>
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<tr>
<td>Voskaridou et al. (table 1 and 4)</td>
<td>131 on HU/199 not on HU</td>
<td>49/995* (4.92 per 100)</td>
<td>13/1048* (1.24 per 100 or 2.00 per 100)</td>
<td></td>
</tr>
<tr>
<td>Steinberg et. al (tables 1 and 3)</td>
<td>44 not on HU/40 on HU (at least 10yrs)</td>
<td>321 and 506, respectively</td>
<td>4.98 per 100 (at least 10yrs on HU vs never on HU)</td>
<td>1.78 per 100 (at least 10 years on HU)</td>
</tr>
<tr>
<td>Hany Elmariah (table 2)**</td>
<td>172/240</td>
<td>Hazard ratio on HU 0.82</td>
<td></td>
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</tbody>
</table>

*Pediatric data; **Duration of HU exposure unknown
Patient years calculated by - number of patients x median follow up; thus 131 x 49; and 5 x 199.
In summary, the preponderance of evidence demonstrates that use of hydroxyurea is associated with:

1. Decreased risk factors for death
   - decrease rate of pain
   - decrease rate of ACS
   - decrease wbc
   - increase Hb F

2. Decreased rate of death in two large adult observational studies and one pediatric study
Benefits and risks of hydroxyurea therapy in SCD

**Benefits**
- Decrease rate of
  - pain
  - acute chest syndrome
  - hospitalizations
  - decreased TCD velocity
- Improved anemia
- Improved quality of life
- Survival advantage

**Risks**
- Myelosuppression
- Risk of fetal abnormalities
- Not curative, does not reverse chronic end-organ damage
- Long term use? Increased risk of cancer
  - Large prospective observational study of 1638 patients with PCV
  - Did not show increased risk of leukemia attributable to hydroxyurea
Our approach

1. We introduce the concept of treating asymptomatic children at age 6 months
2. We go through the handbook with patients and families, talking about pros and cons
3. Medication is started in the out-patients
How we treat

• As standard of care, all children 5yrs or older with HbSS/Sβ⁰-thalassemia are offered hydroxyurea therapy
  • Pediatrics 90% are on hydroxyurea
  • Adults 69% on hydroxyurea
• We offer hydroxyurea to children less than 5yrs with multiple pain or ACS episodes
• Based on increasing evidence, pediatric and adult patients with severe hemoglobin SC disease are started on hydroxyurea therapy.

Hydroxyurea Dosing

• Starting dose 20 mg/kg/day as single dose
• Dose increased every 8-12 weeks by 5mg/kg/day unless toxicity occurred
• Titrate to a goal of 30mg/kg/day
• Folate 1mg/day administered also
Laboratory Monitoring

- CBC with differential
- Reticulocyte count
- Serum Chemistries
- All labs obtained baseline and monthly
- Once maximum tolerated dose achieved, labs obtained bimonthly, then every 2-3 months
Hydroxyurea toxicity

- Hematologic (hemoglobin concentration ≤8.0g/dl, absolute neutrophil count ≤1.5 x 10^9/L, platelet count ≤ x 10^9/L)
- Renal (doubling of serum CR)
- Maximum tolerated dose determined individually, based on toxicity or maximum tolerated dose of 30mg/kg/day
- In presence of toxicity, dose halved until recovery, then resumed at lower dose
Adherence

- Education of patient and family is key
- Discuss consequences of nonadherence
- Frequent medication review, calendars
- Encouragement from family members
- Reviewing blood changes in clinic, like MCV, morphology
Logistical issues

• Lack of adequate outpatient nursing support to manage a chemotherapy agent in a chronic disease population
• Lack of resources to provide education to families about hydroxyurea therapy
• Transportation for necessary follow-up
• Availability of suspension formulation
• Provider knowledge about hydroxyurea
Conclusion

• Morbidity of SCD starts in early childhood and continues throughout the lifespan (concept of asymptomatic disease is misnomer)

• Until the perceived risk: benefit ratio of curative modalities improve (HSCT), hydroxyurea is the best treatment option for asymptomatic children with sickle cell anemia
Thank you!
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