Optimizing Chronic Transfusion Therapy for Survivors of Hemoglobin Barts Hydrops Fetalis

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Dear Editor:

Hemoglobin Barts hydrops fetalis (homozygous $\alpha^0$-thalassemia) results from deletion of all four $\alpha$-globin genes [1]. It was previously considered a universally fatal condition, however, with recent advances in prenatal care and the availability of intrauterine blood transfusions, increasing number of patients are now surviving into adulthood [2]. Similar to patients with transfusion-dependent thalassemia due to $\beta$-thalassemia (TDT-\(\beta\)) these patients require life-long and regular transfusions, as the option of curative stem cell transplant may not be available for the majority of these patients. Although the Thalassemia International Federation guidelines recommend a transfusion strategy similar to TDT-\(\beta\) for these patients [3], no report exists on the optimal transfusion management of patients with homozygous $\alpha^0$-thalassemia, which could be referred to as transfusion-dependent thalassemia due to $\alpha$-thalassemia (TDT-\(\alpha\)). In TDT-\(\beta\), initiation of transfusions results in improvement of anemia and suppression of ineffective erythropoiesis, the main underlying pathophysiologic processes.

In early 2014, we critically reviewed the treatment strategy for four patients with homozygous $\alpha^0$-thalassemia at our institution who were previously on regular blood transfusions to keep their hemoglobin levels above 100 g/L. Research was approved by Institutional Review Board, and patients gave consent in accordance with the Declaration of Helsinki. All patients had significant splenomegaly, progressive peripheral blood reticulocytosis and biochemical markers of hemolysis (high lactate dehydrogenase, aspartate aminotransferase, indirect bilirubin), erythropoiesis (elevated soluble transferrin receptor), and tissue hypoxia (high serum erythropoietin). In addition, three of the four showed brain MRI changes in keeping with “silent” ischemic infarcts [Table-1 and Figure-1].
On further investigation, hemoglobin analysis (by high-performance liquid chromatography (HPLC) and capillary zone electrophoresis) showed hemoglobin H (Hb H) percentage ranging from 24% to 64% in our patients with older patients having higher Hb H. Hemoglobin H, a tetramer of four $\beta$-globin chains, has extremely high oxygen affinity and poor tissue oxygen delivery making it essentially non-functional [4-6]. With the high Hb H levels observed in our chronically transfused patients with homozygous $\alpha^0$-thalassemia, we estimated the patients’ “functional” hemoglobin as \( \text{total hemoglobin} \times (1 - \frac{\text{Hb H\%}}{100}) \), which ranged from 42.7 to 79.0 g/L.

To improve tissue oxygenation and suppress hemolysis, we elected to modify our transfusion strategy by aggressively suppressing endogenous erythropoiesis with a goal to reduce Hb H percentage to less than 15% and to keep the “functional” hemoglobin above 100 g/L in our patients. These targets were chosen to correspond to the average Hb H levels observed in patients with hemoglobin-H disease and the recommended pre-transfusion hemoglobin level in TDT-$\beta$ patients. To achieve these targets, three patients with Hb H levels of more than 25% also required 1 to 4 exchange transfusions (one received one exchange, another received three, and the third patient received four exchange transfusions). One year following the implementation of the new transfusion regimen, we observed a significant and persistent improvement in all hematological and biochemical markers of hemolysis and decreased spleen size in all patients [Table-1 and Figure-1]. Over the course of one year, the new transfusion strategy required a higher total volume of transfusion compared with the standard approach [286 (SD:21) vs. 208 ml/kg/year (SD:14)]. However, over the latest 4 months of the year-long intensive transfusion approach, the volume of transfusion decreased to 258 ml/kg/year (SD:22) when the new steady-state targets for the total pre-transfusion “functional” hemoglobin (> 100 g/L) and Hb H level (< 15%) had been achieved.
A fifth patient, male and homozygous for common Southeast Asian deletion (--SEA/--SEA), was born after the implementation of the new transfusion strategy and has been transfused accordingly since birth. Fourteen months into this new regular transfusion regimen, this patient has normal serum lactate dehydrogenase, aspartate aminotransferase, unconjugated bilirubin, and soluble transferrin receptor levels but continues to have peripheral blood reticulocytosis. The patient has normal growth parameters (age and gender-adjusted height: 58 percentile, z-score 0.20), achieved normal developmental milestones and at the last follow-up, had no splenomegaly. Total volume of transfused packed red blood cell in this patient has been 251 ml/kg/year.

Despite adequate transfusion intensity based on the TDT-β approach, the homozygous α^0^-thalassemia patients showed high Hb H levels in peripheral blood and profound reticulocytosis, suggesting that these patients maintained relatively more effective erythropoiesis (in contrast to ineffective erythropoiesis in their TDT-β counterparts) that was not adequately suppressed by transfusions. This suggests that homozygous α^0^-thalassemia is a predominantly hemolytic disease with a robust erythropoietic response. This is likely due to the fact that Hb H aggregates preferentially in older red blood cells in the peripheral blood, while in TDT-β unpaired α-globin chains form molecular aggregates that lead to apoptosis of erythroblasts early in the process of erythropoiesis in the bone marrow [7]. Our patients with homozygous α^0^-thalassemia who were transfused using the TDT-β regimen had preserved erythropoiesis leading, over time, to increased Hb H levels associated with increased peripheral hemolysis. With the high Hb H percentage, the proportion of “functional” hemoglobin decreased and tissue hypoxia worsened (despite stable “total” hemoglobin) further inducing erythropoiesis.
Suboptimal transfusions (with associated anemia and hypoxia) as well as severe hemolysis have been shown to be associated with a variety of significant clinical sequelae in β-thalassemia patients and in other disorders [8-10]. Here, we demonstrate that in patients with homozygous α<sup>0</sup>-thalassemia (TDT-α), a transfusion strategy similar to those of TDT-β patients does not adequately ameliorate the underlying hemolytic process and the poor tissue oxygen delivery over time, making this approach suboptimal for the management of these patients. While we are yet to demonstrate any long-term clinical benefits to these patients (which would require a longer duration of regular transfusions), a more intensive transfusion regimen targeted at reducing Hb H levels resulting in an increased “functional” hemoglobin, reduced tissue hypoxia and hemolysis seems more appropriate for patients with homozygous α<sup>0</sup>-thalassemia. Splenectomy has been associated with reduced transfusion requirements in TDT-β and improvement in hemoglobin level in hemoglobin-H disease patients with significant splenomegaly [11]. However, in patients with homozygous α<sup>0</sup>-thalassemia, splenectomy, while prolonging survival of transfused Hb A-containing erythrocytes, would likely also prolong the lifespan of endogenous erythrocytes that almost exclusively carry non-functional Hb H. We considered these pathophysiologic differences, in addition to the known long-term complications of splenectomy, to inform our decision not to splenectomize our patients. Recently, an international registry of surviving patients with homozygous α<sup>0</sup>-thalassemia has been established (direct communication, Professor Douglas Higgs, University of Oxford, UK). Clinical data gathered from this registry will be invaluable in shedding light on the long-term clinical benefit of our proposed transfusion strategy compared to standard TDT-β strategy, helping to define optimal care for patients with homozygous α<sup>0</sup>-thalassemia.

The intensive transfusion strategy comes with a price: increased transfusional iron burden which requires escalation of iron-chelation therapy, posing significant challenges with treatment
costs and patient adherence. Whether these drawbacks can be offset by better longer-term clinical outcomes of patients with homozygous $\alpha^0$-thalassemia remains to be proven.

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Conflict of Interest:
All authors report no pertinent conflict of interests.

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Author’s Contribution:
AA designed research. AA, WB, MK and IO performed research. AA and SC analyzed data. AA and IO wrote the initial version of the paper. All authors reviewed the paper and confirmed this final version.

References


### Table 1

**Patients’ Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the time of implementation of new transfusion strategy</td>
<td>6 years</td>
<td>16 years</td>
<td>15 years</td>
<td>14 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Alpha globin gene deletion</td>
<td>-- SEA/--SEA</td>
<td>-- SEA/--SEA</td>
<td>-- SEA/--SEA</td>
<td>-- SEA/--SEA</td>
</tr>
<tr>
<td>Proportion of Hb H before implementation of new transfusion strategy (%) (^1)</td>
<td>24</td>
<td>64</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>Calculated functional hemoglobin before new transfusion strategy (g/L)</td>
<td>79.0</td>
<td>42.7</td>
<td>52.0</td>
<td>59.3</td>
</tr>
<tr>
<td>Endocrine abnormalities</td>
<td>None</td>
<td>-Diabetes mellitus</td>
<td>-Hypogonadism</td>
<td>-Hypogonadism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Delayed puberty</td>
<td>-Hypothyroidism</td>
<td>-Growth hormone deficiency</td>
</tr>
<tr>
<td>Bone disease (lumbar Z-score &lt; 2.0)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Short stature (height Z-score &lt; 2.0)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MRI changes compatible with silent ischemic infarct</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Other complications</td>
<td>None identified</td>
<td>-Gout</td>
<td>None identified</td>
<td>Gall Stones</td>
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<tr>
<td></td>
<td></td>
<td>-Systemic lupus erythematosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Bleeding tendency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen size (cm) (^2)</td>
<td>Before intervention</td>
<td>12.0</td>
<td>19.1</td>
<td>16.0</td>
</tr>
<tr>
<td></td>
<td>One year after intervention</td>
<td>10.2 (normal for age)</td>
<td>17.8</td>
<td>14.1</td>
</tr>
<tr>
<td>Serum erythropoetin level (mU/ml)</td>
<td>Before intervention</td>
<td>252.0</td>
<td>421.0</td>
<td>709.0</td>
</tr>
<tr>
<td></td>
<td>One year after intervention</td>
<td>46.3</td>
<td>93.4</td>
<td>31.4</td>
</tr>
</tbody>
</table>

Characteristics of four homozygous \(\alpha^0\)-thalassemia patients who are being followed in our institution. All patients provided consent for publication of this report. One patient (data not shown) was born after the implementation of new transfusion strategy and has been transfused based on the new regimen since birth.

1. Patients’ hemoglobin analysis was performed via high performance liquid chromatography (HPLC) and confirmed using capillary zone electrophoresis. 2. Spleen size was measured on ultrasonography.

Hb: Hemoglobin, MRI: magnetic resonance imaging. SEA: Southeast Asian deletion.
**Figure Legend**

**A)** The trend in the pre-transfusion reticulocyte count (%) in four patients with homozygous $\alpha^0$-thalassemia on standard transfusion therapy *before* commencement of new transfusion regimen. The dashed line represents LOESS fit line with 95% confidence bands. **B)** The trend in the pre-transfusion Hb H level in peripheral blood. The dotted line represents the 15% target. **C-F)** The trends in pre-transfusion unconjugated bilirubin, soluble transferrin receptor (STR), lactate dehydrogenase (LDH) and reticulocyte count. Shaded areas indicate laboratory results before the implementation of new transfusion regimen (Day 0). The dotted lines represent upper boundaries of normal values. We used repeated measure ANOVA to examine the association between intervention and biochemical or hematologic outcomes. Overall, intervention effect was significant for all laboratory outcomes. Moreover the effects of intervention on improvement of outcomes remained persistent for each of the post-intervention time brackets (0-120, 121-240 and 241-365 days). Eight to 12 months after the intervention, the average lactate dehydrogenase [964.37 (SD: 239.85) vs 2736.75 (SD: 242.44)], indirect bilirubin [22.03 (SD: 5.53) vs 57.38 (SD: 10.45)], soluble transferrin receptor [2.15 (SD: 0.58) vs 7.31 (SD: 0.91)], and reticulocyte count [354.22 (36.42) vs 631.87 (SD: 82.54)] were all significantly lower compared to pre-intervention. **G-H)** Associations of “functional” hemoglobin with STR, and Hb H level with LDH. Dotted lines represent target values for functional hemoglobin and Hb H%, as well as the upper boundaries of normal values for LDH and STR. [See Supplementary Material for the details of statistical analysis].
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