Dependance on chronic transfusion

Pr Saliou Diop
Hematology – Blood transfusion

Dakar- Sénégal

diop@cnts-dakar.sn
Introduction

• Chronic transfusion: Regular use of blood transfusion in patients with chronic disease

• Standard treatment in many pathological situations

• Complications are frequent, infectious or others
Core Topics

1. Indications of chronic transfusion
2. Modalities of chronic transfusion
3. Complications
4. Alternatives to chronic transfusion
1- Indications of chronic transfusion

- Sickle cell disease
- Major thalassemia
- Myelodysplastic syndromes
- Bone marrow failure
Sickle cell disease in Africa

- 10 -30 % HbS carriers
- 220 000 newborns with SCD
- 16 % causes of under 5 years mortality in some countries
Blood transfusion and SCD

Simple transfusion in acute anemia
- Acute hemolysis
- Splenic sequestration
- Parvovirus infection

Curative punctual RBC exchange
- Stroke
- Acute chest syndrom (ACS)
- Hepatic sequestration
- Sepsis
- No resolutive vaso occlusive crisis
- No resolutive priapism

Preventive punctual RBC exchange
- Prevention to Surgery
- Preparation to a long trip
- Pregnancy

Chronic RBC transfusion
- Recurrent VOC or ACS if Hydroxyurea is not possible
- Recurrent leg ulcers
- Recurrent Priapism
- Multiple organ failure
- Stoke antecedent
- Abnormal DTC
Chronic transfusion can prevent cerebrovascular accidents in children with high velocity in cerebral arteries early detected by transcranial Doppler.
Chronic transfusion and prevention of stroke in SCD

Major Thalassemia

- Evaluation of severity depends on the patient blood transfusion requirements

- Objective: maintain Hb level > 9-10 g/dl

- Transfusion program:
  - packed red cells around 15 ml/kg/week
  - or 20 ml/kg/ 4 weeks

- Results: Improve morbidity and overall survival of patients
Myelodysplastic syndromes

• Range of conditions in which stem cells do not mature into healthy blood cells.

• Most MDS patients become anemic and require chronic RBC transfusion as support therapy

• Patients are also immunosuppressed and neutropenic and therefore potentially exposed to risks related to each transfusion
Variables influencing the indication and extent of RBC support in MDS patients
Bone marrow failure

- **Quantitative bone marrow insufficiency** related to complete or partial absence of hematopoietic tissue and no abnormal cells.

- **Chronic transfusion** could be the standard care in absence of curative one as hematopoietic stem cell transplantation

- **Blood products**
  - RBC concentrates
  - Platelet concentrates
2. Modalities of chronic transfusion

• Simple transfusion

• Manual transfusion exchange

• Automated transfusion exchange
Modalities of chronic transfusion

- **Simple Transfusion**
  risk of hyperviscosity and iron overload

- **Manual transfusion exchange transfusion**
  
  - 2 peripheral venous access
  - 3 steps:
    - Bleeding of 10 -15 ml/kg and perfusion in same time of isotonic solution
    - Transfusion in same debit than bleeding
    - Stop bleeding when required volume is reached and continue transfusion in rapid debit
  - Manual exchange with only one venous access in young baby
## Erythrocytapheresis (ECP)

<table>
<thead>
<tr>
<th>Limits</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More expensive</td>
<td>• Isovolumetric transfusion (less risk of hyperviscosity)</td>
</tr>
<tr>
<td>• Require specialized equipment and trained personnel</td>
<td>• More effective in lowering Hb S in SCD</td>
</tr>
<tr>
<td>• Increased blood exposure compared to simple transfusion (30-50 % more RBC units)</td>
<td>• Can limit iron overload</td>
</tr>
<tr>
<td></td>
<td>• Lower alloimmunisation ?</td>
</tr>
<tr>
<td>Transfusion regimen</td>
<td>Patients with any new antibody, n (%)</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>ECP, n = 22</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Simple transfusion, n = 23</td>
<td>4 (18)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
</tr>
</tbody>
</table>
3. Chronic transfusion risks

1. Transmission of infectious agents
2. Immunologic risks
3. Iron overload
4. Others risks
Infectious risks

- **High prevalence infectious agents**
  - HIV
  - HBV
  - HCV
  - Syphilis

- **No screened infectious agents**
  - Plasmodium
  - HTLV 1

- **No relevant used techniques**
Immunological complications

• Allo-immunisation
  – immediate and delayed hemolytic transfusion reactions
  – delays and difficulties in locating compatible blood

• Allo-immunisation prevention
  – In blood donors: ABO and Rh grouping
  – In chronically transfused patients
    • Irregular antibody screening
    • Compatibility testing
  – Phenotyped RBC (genotyping technology)
Immunologic risks (positive antibody in SCD patients)

- Diop S (Dakar, 2008) 8.3%
- Norol F (France, 1994) 30.6%
  PSL RH-K compatible: 8.2%
- Aygun (USA, 2002): 29 % (enfants)
  47 % (adultes)
- Murao (Brésil, 2005): 9.9 %
Iron overload

• No mechanism of physiological elimination of body iron

• 1 RBC unit 200 - 250 mg of iron

• Transfusion of 2 RBC unit is equivalent to iron intestinal absorption from food during one year

• Iron overload is ineluctable during chronic transfusion (10-20 transfusions)

A Normal Iron Supply and Storage

B Sickle Cell Anemia

C Sickle Cell Anemia with Long-Term Red-Cell Transfusion

D Sickle Cell Anemia with Transfusion and Iron-Chelating Therapy
# Evaluation of iron overload

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td><strong>Accessible</strong>, low cost</td>
<td>- Indirect measure for iron stock</td>
</tr>
<tr>
<td></td>
<td>- Positive Correlation positive with morbidity and mortality</td>
<td>- Increase with <em>inflammation</em>, hepatic cytolysis</td>
</tr>
<tr>
<td></td>
<td>- Repeated tests for treatment monitoring</td>
<td>- Only one measure is not reliable</td>
</tr>
<tr>
<td>Iron hepatic concentration measured after hepatic biopsy</td>
<td><strong>Direct measure</strong> of iron hepatic concentration</td>
<td>- <em>invasive</em> technique</td>
</tr>
<tr>
<td></td>
<td>- Quantitative, good sensibility and specificity, validated standard</td>
<td>- Inadequate for follow up</td>
</tr>
<tr>
<td></td>
<td>- Positive correlation with morbidity and mortality</td>
<td>- Inter-laboratory variations</td>
</tr>
<tr>
<td></td>
<td>- Give information on hepatic histopathology</td>
<td></td>
</tr>
</tbody>
</table>
# Evaluation of iron overload

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic IRM R2</strong></td>
<td>- Good correlation with hepatic iron concentration</td>
<td>- High cost and need a special software</td>
</tr>
<tr>
<td></td>
<td>- Hepatic and cardiac iron overload measured simultaneously</td>
<td>- General anesthesia for infants</td>
</tr>
<tr>
<td></td>
<td>- Adequate for regular follow up</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac IRM cardiaque T2</strong></td>
<td>- Reproducible evaluation of heart iron</td>
<td>- High cost and need a special software</td>
</tr>
<tr>
<td></td>
<td>- Heart functional parameters are evaluated simultaneously</td>
<td>- General anesthesia for infants</td>
</tr>
</tbody>
</table>
Iron overload

**Consequences**
- Long time asymptomatic
- Hepatic iron overload: first involved organ
- Cardiac overload: principal cause of death
- Endocrinopathies
- Arthropathies

**Treatment**
- After 10-20 transfusions of RBC units
- Serum ferritin > 1000 ng/ml
- Iron hepatic concentration > 3-7mg de fer /g dry weight
## Iron chelating agents

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>DEFEROXAMINE Desferal®</th>
<th>DEFERASIROX Exjade®</th>
<th>DEFERIPRONE Ferriprox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage (mg/kg/jour)</td>
<td>25 - 50</td>
<td>24 - 40</td>
<td>75 - 100</td>
</tr>
<tr>
<td>Administration</td>
<td>SC or IV 8 – 10 h/j 5-7 days/week.</td>
<td>Per os 1 time/day</td>
<td>Per os 3 times /day</td>
</tr>
<tr>
<td>Plasmatic half life</td>
<td>20 – 30 mn</td>
<td>8 – 16 hours</td>
<td>2 – 3 hours</td>
</tr>
<tr>
<td>Elimination</td>
<td>Biliiar and urines</td>
<td>biliar</td>
<td>urines</td>
</tr>
<tr>
<td>Indications</td>
<td>Overload by transfusion</td>
<td>Overload by transfusion</td>
<td>Overload by transfusion In thalassemic patients</td>
</tr>
<tr>
<td>Side effects</td>
<td>Irritation on injection site, occul and auditive troubles, growth delay, allergic reaction, détresse respiratoire</td>
<td>digestive and renal disfunction</td>
<td>Agranulocytosis, digestive troubles, arthropathies, hépatic dysfunction,</td>
</tr>
</tbody>
</table>
Others risks

• Venous access

• Allergic or anaphylactic transfusion reactions
  – Not fatal but can cause substantial discomfort

• Transfusion-related acute lung injury

• Syndromes frisson-hyperthermie
  – Leucodepleted blood components

• Negative impact on overall survival
4. Alternatives to chronic transfusion

- Curative treatment of pathologies
  - Sickle cell disease:
    - Hematopoietic stem cell transplantation
    - Hydroxyurea, an alternative to chronic transfusion
  - Thalassemia: 30% reduction of blood requirements with splenectomy
  - Bone marrow failure: Hematopoietic stem cell transplantation
  - Myelodysplasia: Demethylating agents

- Treatment of erythropoisis stimulating agents
- Patient Blood Management
Hydroxyurea and SCD

(a) Patients with HbS/β⁰ thalassemia and hydroxyurea exposure had improved 10-year overall survival (OS) compared to patients without hydroxyurea exposure (87 vs. 54%, P = 0.001); (b) HbSS patients receiving hydroxyurea had a 10-year OS of 100% compared to 10% in those without hydroxyurea exposure (P < 0.01). Adapted from [25**].

Voskaridou E et al., Blood, 2010, 115
Hydroxyurea: Mechanism of action

1. Induction of fetal hemoglobin in erythroid compartment; 2. marrow cytotoxicity and decreased neutrophil and reticulocyte counts; 3. altered expression of adhesion molecules on circulating neutrophils and reticulocytes decreases adhesiveness and subsequent endothelial damage; 4. macrocytosis and increased hydration reduces hemolysis and intracellular sickling; 5. local release of nitric oxide (NO) results in vasodilation.

Reproduced from [20**].
**Hydroxyurea réduces the risk of stroke but less than chronic transfusion**

**TABLE I. Incidence and Rate of Secondary (Recurrent) Stroke in Children With SCA, by Therapeutic Intervention Following the First Stroke Event**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year [Refs.]</th>
<th># Patients</th>
<th>Recurrence (%)</th>
<th>Secondary stroke rate per 100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moohr et al.</td>
<td>1982 [20]</td>
<td>14</td>
<td>83</td>
<td>54</td>
</tr>
<tr>
<td>Chronic transfusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moohr et al.</td>
<td>1982 [20]</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Russell et al.</td>
<td>1984 [21]</td>
<td>20</td>
<td>14</td>
<td>2.0 (estimated)</td>
</tr>
<tr>
<td>Pegelow et al.</td>
<td>1995 [22]</td>
<td>61</td>
<td>15</td>
<td>4.8</td>
</tr>
<tr>
<td>Ohene-Frempong et al.</td>
<td>1998 [2]</td>
<td>72</td>
<td>14</td>
<td>6.4</td>
</tr>
<tr>
<td>Scothorn et al.</td>
<td>2002 [23]</td>
<td>137</td>
<td>23</td>
<td>2.2</td>
</tr>
<tr>
<td>Ware et al.</td>
<td>Unpublished</td>
<td>44</td>
<td>11</td>
<td>3.3</td>
</tr>
<tr>
<td>Transfusion discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moohr et al.</td>
<td>1982 [20]</td>
<td>7</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Rana et al.</td>
<td>2001 [24]</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Change from transfusions to hydroxyurea prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ware et al.</td>
<td>1999 [15]</td>
<td>15</td>
<td>33</td>
<td>6.8</td>
</tr>
<tr>
<td>Ware et al.</td>
<td>2004 [16]</td>
<td>21</td>
<td>10</td>
<td>3.1</td>
</tr>
<tr>
<td>Ware et al.</td>
<td>2004 [16]</td>
<td>36</td>
<td>19</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*Subjects who had an abrupt discontinuation of transfusions; Subjects with an overlap period of transfusions and hydroxyurea; All subjects who switched from chronic transfusions to hydroxyurea therapy for secondary stroke prophylaxis.*

*Pediatr Blood Cancer DOI 10.1002/pbc*
CONCLUSION

• Chronic transfusion dependance is associated with elevated risks of transfusion related incidents and accidents

• Disponibility and quality of blood products are capital

• The major goal is to develop alternatives by preventing or treating diseases associated with chronic transfusion by innovative means