Acquired aplastic anemia / Fanconi

André Tichelli

Special thanks to
- Régis Peffault de Latour
- Gérard Socié
- Judith Marsh
At the end of this presentation you should know

- why aplastic anemia is a particular disease within EBMT
- what we can expect from HSCT and from immunosuppressive treatment
- what changes will occur in near future in the approach of patients with acquired aplastic anemia
Definition of aplastic anemia (AA) and severity of the disease

- Persistent and unexplained pancytopenia
- With marrow aplasia
- There is no specific marker

SAA (severe AA)
- at least 2/3 criteria:
  - ANC < 0.5x10⁹/L
  - Platelets < 20x10⁹/L
  - Reticulocytes (microsc.) < 20x10⁹/L
  - Reticulocytes (auto) < 60x10⁹/L

vSAA (very severe AA)
- ANC < 0.2x10⁹/L

moderate AA
- not fulfilling criteria of SAA
  - ANC > 0.5x10⁹/L
Aplastic anemia is an immune-mediated T-cell destruction of the marrow

- Cytotoxic T cell expansion
- Expressing cytokines (g-INF)
- Oligoclonal expansion (immunodominant clonotypes)
- Decrease of the hematopoietic stem cell pool

We do not know what is the trigger of the T cell proliferation
Two first-line treatment options for SAA: Both improved with time

**Matched related BMT**
- Exchanges the whole lympho-hematopoietic system
- Curative treatment
- But risk of GVHD

**Immunosuppression**
- Attacks or modulates immune-reactive T cells
- Not curative treatment
- Risk of clonal evolution

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SAA EBMT Registry, updated 2012
Previous decision algorithm for first-line treatment

```
  SAA
   Age
   < 40 yr
     HLA identical sibling donor
       Yes
         HSCT
       No
   > 40 yr
     IS
```

Marsh J. ASH 2006
Questions to stem cell transplantation

- First line treatment with a matched sibling donor
  1. What are the main obstacles?
  2. Which source of stem cells?
  3. Which conditioning regimen?
  4. Which prophylaxis for GVHD?
  5. What is the influence of the age of the patient?
Graft rejection and GVHD are the main obstacles of HSCT in SAA - related to age

$p<0.0001$  
$p<0.0001$
Bone marrow has to be preferred to peripheral blood in any case

![Graph showing survival probability over months comparing BM (N = 722) and PB (N = 151).]

- **BM (N = 722)**
- **PB (N = 151)**

**Survival Probability, %**

**MOTHS**

- **P = 0.02**

Schrezenmeier al Blood 2007; 110:1397-1400
GVL effect is not needed and GVHD is harmful
ATG is a favorable predictor of outcome

- For BMT and PBPC
- Especially in patients >20 years

Conditioning with Cy and ATG improves survival

The use of CSA and MTX is associated with improved survival in patients with SAA who receive transplant from a matched sibling donor.
Influence of age on 10-year survival in HLA identical siblings

OS survival at 5 years
n=4267

Age groups
<=20  79%
>20   73%
>30   68%
>40   61%
>50   46%

Days since Transplantation
Causes of death according to age of the patients

Unpublished data from the SAA EBMT WP
Can we solve the problem of age in aplastic anemia?

- Trend of lower graft failure: 0% vs 11%, p=0.09)
- No difference in incidence of GVHD

n = 30; median age 46 (31-66)
n = 239; median age 39 (30-67)
For first line treatment, of patients without matched sibling donor

1. Which is the standard immunosuppressive treatment?
2. Which ATG should be used?
3. What is the influence of the age of the patient?
4. Does any adjunct to standard treatment improve the results?
5. What are the main obstacles?
Combination ATG and CSA is the gold standard for IS in SAA

**Event-free survival**
Non-responders could cross-over

**Overall survival**
Non-responders did not receive a second-line treatment

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Event-free survival

Years since Immunosuppression

Cumulative Survival

Months from treatment

Frickhofen N et al. Blood. 2003; 101:1236-1242

## Treatment of non-severe aplastic anemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSA N=61</th>
<th>ATG+CSA N=54</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>28 (46%)</td>
<td>40 (74%)</td>
<td>.02</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>9.7 (4.2-14.9)</td>
<td>11.8 (2.5-15.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1.6 (0.5-9.6)</td>
<td>11.8 (0.3-24)</td>
<td>.4</td>
</tr>
<tr>
<td>Platelets</td>
<td>29 (3-182)</td>
<td>84 (5-216)</td>
<td>.005</td>
</tr>
<tr>
<td>2. ATG*</td>
<td>15 (25%)</td>
<td>3 (6%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Alive failure free</td>
<td>41 (67%)</td>
<td>49 (90%)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Horse ATG provides better outcome than rabbit ATG

- Randomized prospective trial with 120 patients
- Response at 6 months (68% vs 37%), and overall survival at 3 years (96% versus 76%) was largely in favor of horse ATG
- 4 death in the horse and 14 death in the rabbit ATG group

<table>
<thead>
<tr>
<th>Cause of death (11/35)</th>
<th>Time to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis (5)</td>
<td>9,210,243,326,370</td>
</tr>
<tr>
<td>Pneumonie (2)</td>
<td>207; 209</td>
</tr>
<tr>
<td>Sepsis &amp; multiorgan failure</td>
<td>6</td>
</tr>
<tr>
<td>Sepsis &amp; cardiac arrest</td>
<td>148</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>288</td>
</tr>
<tr>
<td>Post-SCT fungal infection</td>
<td>390</td>
</tr>
</tbody>
</table>

Scheinberg P. et al. NEJM. 2011; 365:430-438
Influence of the age on outcome of immunosuppressive treatment

- No age difference for response and relapse rate
- Higher death rate in older age

Based on data from the G-CSF study (Tichelli A. et al. Blood 2011;117:4434-4441)

death rates in G-CSF study
- 15% in < 60 years
- 41% in ≥ 60 years
## Can we improve result in first-line immunosuppressive treatment

<table>
<thead>
<tr>
<th>Type</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG + CSA + G-CSF *</td>
<td>No difference in response or survival</td>
</tr>
<tr>
<td>ATG + CSA + GM-CSF and EPO</td>
<td>No difference in response or survival</td>
</tr>
<tr>
<td>ATG + CSA + Mycophenolate</td>
<td>No difference in response or survival</td>
</tr>
<tr>
<td>ATG + CSA + Sirolimus</td>
<td>No difference in response or survival</td>
</tr>
<tr>
<td>Alemtuzumab alone#</td>
<td>Low response rate (19%); increase in early deaths; study has to be discontinued</td>
</tr>
</tbody>
</table>

*Tichelli et al. Blood 2011
Teramura et al. Blood 2005
Glukcmann et al. BJH 2002

Thrombopoietin receptor agonist (Eltrombopag) for aplastic anemia

- Non-randomized study on 25 SAA patients
  - refractory to IS
  - transfusion dependent for platelets
- 11/25 had hematological response, 9/11 became transfusion-independent for platelets
- Follow-up study
  - overall response in 17/43 patients (40%)
- In 5 patients with robust response the drug was discontinued
  - all maintained stable counts
  - median 13 months off eltrombopag

Multi-lineage hematological responses to eltrombopag

Olmes MJ et al. NEJM. 2012; 367:11-9
Desmond R et al. Blood 2014;123:1818-1825
# Obstacles of immunosuppressive therapy

<table>
<thead>
<tr>
<th>Obstacle</th>
<th>Remark</th>
<th>Outcome and treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed hematopoietic reconstitution</td>
<td>Response at 2 to 6 months, sometimes later</td>
<td>Prolonged risk of infection and bleeding</td>
</tr>
<tr>
<td>Relapse</td>
<td>Relapse rate between 25 and 40% at 5 years</td>
<td>Relapses are re-treatable</td>
</tr>
<tr>
<td></td>
<td>Good prognosis</td>
<td></td>
</tr>
<tr>
<td>Primary refractory to immunosuppression</td>
<td>10-20% no marker for refractory disease at diagnosis</td>
<td>Very poor prognosis alternative treatment needed</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Clonal evolution of PNH</td>
<td>25% of the patients have a PNH clone at diagnosis</td>
<td>Treatment with eculizumab?</td>
</tr>
<tr>
<td></td>
<td>A small proportion can develop full PNH after IS</td>
<td></td>
</tr>
<tr>
<td>Clonal evolution into MDS/AML</td>
<td>20-25% at 10 years</td>
<td>Poor prognosis, treatment option as for primary MDS/AML</td>
</tr>
</tbody>
</table>

- Problems mainly due because immunosuppression is not a curative treatment
Alternative donor for patients refractory to IS without a matched sibling donor

- Improvement of transplantation procedure
- Better donor selection (genetic HLA-matching)
- Different conditioning regimens
  - Cyclophosphamide, Fludarbine, ATG ± TBI (2Gy)
What we should know about Fanconi anemia

- Inherited disease with physical anomalies and marrow failure syndrome; these patients have a high risk of secondary malignancy
- Genetic instability leading to an abnormal DNA repair
- The treatment approach is completely different to the treatment of acquired aplastic anemia

### Diagnostic particularities

<table>
<thead>
<tr>
<th>Physical anomalies</th>
<th>However these anomalies are not observed in all Fanconi patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis usually performed between the age of 6 and 8 years</td>
<td>However can sometimes be made in young adult patients</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>Often moderate and concerning one to all three cell lines In some the patients pancytopenia may become very severe</td>
</tr>
</tbody>
</table>
Treatment options

- Hematopoietic stem cell transplantation
  - Type of BMT (donor)
    o MSD; however the sibling should not have Fanconi genetic anomaly
    o MUD; results are greatly improving
    o Haplo-HSCT (without post-transplant Cy), still experimental
  - Different conditioning regimen (DNA repair)
    o Cyclophosphamide in lower dose
    o Fludarabine has promising results

- Immunosuppression (ATG and CSA)
  - does not work

- Androgens
  - show some response (50%)
Best prognosis

- Transplant are performed before the age of 10 years
- With fludarabine conditioning regimen
- Low GVGD; lower risk of secondary squamous cell carcinoma

Fanconi anemia patients should be referred to specialized centers

Long-term outcome, mainly affected by secondary malignancies and chronic GVHD

Severe Aplastic Anemia

MSD ≤ 40 years

- BMT
  - Cy-ATG
  - CSA-MTX

< 30 years
- Upfront 10/10 MUD
- BMT

Repeat ATG + CSA

No MSD or >40 years

horse ATG + CSA

Relapse

10/10 HLA MUD and <30 years
- BMT
- Cy-ATG-flu-TBI 2Gy

No 10/10 MUD or >30 years
- 2nd IST (Eltrombopag)

Refractory disease

Experimental BMT
- MUD (one mismatch?)
- Haploidentical Cordblood
Thank you very much for your attention