Severe Aplastic Anemia in Children and Adolescents

Brigitte Strahm

21. April 2018
Acquired Aplastic Anemia in children

What is acquired aplastic anemia?

**Definition**

To qualify as severely aplastic, patients had to have at least two of the following three peripheral blood values: (1) granulocytes < 500/cu mm (2) platelets < 20,000/cu mm and (3) reticulocytes < 1% (corrected for hematocrit). In addition, the marrow had to be either markedly hypoplastic (< 25% of normal cellularity) or moderately hypoplastic (25%–50% of normal cellularity with < 30% of remaining cells being hematopoietic) as estimated from biopsies.

Camitta, Blood 1976

How A.L.G. acts is unknown, but our findings accord with the hypothesis that, in a substantial proportion of cases of aplastic anaemia, unspecified autoimmune reactions block the development of residual stem cells.

Speck, Lancet 1977

Patients presenting with cytopenia and fitting the above criteria may be affected with different conditions that must be excluded before establishing a diagnosis of idiopathic aplastic anemia. All patients should be studied to rule out hypoplastic myelodysplasia/leukemia, congenital marrow failure, infections, and Paroxysmal Nocturnal Haemoglobinuria (PNH).

Dufour, Int J Hem 2015
(Pan)cytopenia in children
Diagnostic and therapeutic Challenges

- PNH
- RCC
- SAA
- IBMF

- acquired
- immune-mediated
- genetic
- inherited
Aquired Aplastic anemia in children

Diagnostic tools

- Family history: hematological disease, cancer predisposition
- Clinical assessment: short stature, failure to thrive, dysmorphic features (microcephaly, face, skeletal), organ malformations (heart, GU)
- Bone marrow aspirate and biopsy
- Cytogenetics
- PNH
- Lymphocyte subpopulations, immunoglobulins, autoantibodies
- Functional test to exclude IBMF i.e. FA/DC
- Molecular Genetics
Aquired Aplastic anemia in children

Exclusion of IBMFS: BSH Guidelines

1) Chromosomal breakage test (diepoxybutane stress test) for Fanconi anaemia.

2) Telomere length by flow cytometry-fluorescence in situ hybridisation (Flow-FISH) to identify patients with dyskeratosis congenita (DC), although it is noteworthy that not all DC patients will have very short telomeres.
Aplastic Anemia in children
Possibility of undiagnosed inherited bone marrow failure syndrome?

- Fanconi Anemia
  
  **RCC:** 15% patients diagnosed with FA, 8% without typical clinical signs
  
  Yoshimi, BJH 2012

  30-40% of patients with FA without obvious clinical evidence
  
  Shimamura, Alter, Blood Reviews 2010

  → Exclusion by chromosomal breakage/growth arrest mandatory

- Dyskeratosis congenita
  
  **RCC:** 5% Patienten mit Mutationen mit Dyskeratosis Congenita assoziierten Genen
  
  Ortmann, Haematologica 2006, Wlodarski/Karow, unpublished

  → Telomere length measurement mandatory?
Telomere and AA: Recognizing underlying DC?
Screening patients with SAA for short telomeres?

Mutations in TERT, the Gene for Telomerase Reverse Transcriptase, in Aplastic Anemia

Hiroki Yamaguchi, M.D., Rodrigo T. Calado, M.D., Ph.D., Hinh Ly, Ph.D., Sachiko Kajigaya, Ph.D., Gabriela M. Baerlocher, M.D., Stephen J. Chanock, M.D., Peter M. Lansdorp, M.D., Ph.D., and Neal S. Young, M.D.

Telomere length < 1 P
- highly sensitive for DC
- not specific for DC

Du, Blood 2009
Telomere and AA: Recognizing underlying DC?

Telomere length in dyskeratosis congenita

Alter, Haematologica 2015
Telomere and AA: Recognizing underlying DC?
Telomere length in other BMFS

Alter, Haematologica 2015

9 · 21. April 2018
EWOG-SAA 2010

Preliminary result of telomere length measurements in EWOG-SAA 2010 (n=77)

Telomere length (qPCR)

Screening of TERC, TERT, DKC1 and TINF2 negative.
Telomere biology
Mechanisms of telomere attrition

A. Normal
- HSC: Hematopoietic stem cell
- Telomerase complex
- Telomere maintenance

B. Germline telomere disease
- Impaired genes: DKC1, NOP10, TERT, NHP2, TERC, WRAP53, TINF2, CTC1, RTE1
- Telomere loss

C. Regenerative stress
- Cell loss/increased mitotic activity
- Telomere loss

D. DNA damage
- ROS: Radiation, toxins, inflammation
- Telomere loss

Townsley, Blood 2014

11 - 21. April 2018
Telomeres and AA: Recognizing underlying DC?
Screening patients with SAA for short telomeres?

Dyskeratosis congenita:

The diagnosis can be made in the clinic examining room, based on a good personal and family history and even a cursory physical examination. Patients may make their own diagnosis using the Internet—better than subspecialists who do not query outside their organ system of interest.

A telomeropathy should be considered in all patients with AA or hypoplastic MDS, and testing should be performed when treatment decisions might be affected.

Townsley, Blood 2014
Aquired Aplastic anemia

Exclusion of IBMFS: BSH Guidelines

1) Chromosomal breakage test (diepoxybutane stress test) for Fanconi anaemia.
2) Telomere length by flow cytometry-fluorescence in situ hybridisation (Flow-FISH) to identify patients with dyskeratosis congenita (DC), although it is noteworthy that not all DC patients will have very short telomeres.
3) Lymphocyte subset testing to identify the presence of B cell lymphopenia; the detection of B cell lymphopenia or monocytopenia, should trigger GATA2 genetic testing (Ganapathi et al, 2015).
4) Next Generation Sequencing (NGS) panels in bone marrow failure to identify cryptic mutations. Screening of children and young people with idiopathic aplastic anaemia in one series identified germline bone marrow failure mutations in in 5·1% of cases (Keel et al, 2016). However, NGS bone marrow failure panels are currently unable to provide results in a timely manner (turnaround time typically 2–4 months). Nevertheless, a positive result could subsequently affect genetic counselling and cancer surveillance, and thus samples should be sent where possible at diagnosis.
Aplastic Anemia in children

Detection of germline mutations to identify underlying IBMF

- Identification of germline variants in children with AA (n=98)

Table 1. Clinical and genetic features of AA patients.

<table>
<thead>
<tr>
<th>D</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Gene</th>
<th>Mutation</th>
<th>Family history**</th>
<th>Physical anomalies</th>
<th>IST</th>
<th>Sibling donor</th>
<th>Post-transplant complications</th>
<th>Time from transplant until death (months)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA3</td>
<td>M</td>
<td>33</td>
<td>DKCI</td>
<td>T66A</td>
<td>4 brothers with clinical DC; early cancers in family</td>
<td>Nail dystrophy, hyperpigmented macules</td>
<td>-</td>
<td>+</td>
<td>Colon cancer</td>
<td>21</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>AA25</td>
<td>F</td>
<td>1</td>
<td>MPL</td>
<td>R102P/W515X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed to engraft initial cord transplant, engrafted 2nd transplant; BOOP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AA37</td>
<td>F</td>
<td>7</td>
<td>MPL</td>
<td>P394S/P394S</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AA45</td>
<td>M</td>
<td>9</td>
<td>DKCI</td>
<td>c.-142 C&gt;G</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AA79</td>
<td>M</td>
<td>6</td>
<td>TP53</td>
<td>R196Q</td>
<td>-</td>
<td>Facial hyperpigmentation</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Age at transplant; **family history indicates family history of related phenotype or cancer in first- or second-degree relative. AA, Idiopathic acquired aplastic anemia; IST: immunosuppressive therapy; DC: dyskeratosis congenita; BOOP: bronchiolitis obliterans organizing pneumonia. Two of the 98 AA patients were included among the pediatric and adult patients with marrow failure or MDS deemed to have idiopathic disease after laboratory and clinically-directed genetic evaluation in the report by Zhang et al. 19 (AA92/FH-50 and AA87/FH-13).

Keel, Haematologica 2016
Acquired Aplastic Anemia

Somatic mutations and clonal hematopoiesis – link to immune pathology

Yoshizato, NEJM, 2015
Acquired Aplastic Anemia

Clonal hematopoiesis with CNN 6pLOH

Figure 1. Copy number changes and allelic imbalances in 46 of the 306 AA cases. The copy number changes and allelic imbalances (or CNN-LOHs) in each case are summarized in the chromosomal order vertically for 46 AA cases with copy number abnormalities. Gains and losses, as well as CNN-LOHs, are shown in the indicated colors.

Katagiri, Blood 2011
Acquired Aplastic Anemia

Somatic HLA mutations

Key Points

- Somatic HLA class I gene mutations are frequent in aAA and define HLA class I restricted autoimmunity in aAA.

- HLA alleles targeted by inactivating mutations are overrepresented in aAA and correlate with poor therapy response and clonal evolution.

Babushok, Blood Adv 2017, Stanley BJH 2017
Acquired Aplastic Anemia

Somatic HLA mutations

Figure 2. Age-related dichotomy of clonal hematopoiesis in aAA, manifested as frequent HLA loss in younger patients and as MDS-associated somatic mutations in older patients. A bubble scatter plot of somatic mutation analysis of the 17 patients with 1 of the 4 HLA risk alleles (HLA-A*33:03, HLA-A*68:01, HLA-B*14:02, or HLA-B*40:02); each patient is represented by a circle. The number of somatic nonsynonymous coding and regulatory region mutations identified by comparative WES is plotted on the y-axis, with the corresponding patient’s age at aAA diagnosis plotted on the x-axis; duration of disease at sequencing is depicted as the area of each point. PNH clones are not shown. Patients with HLA loss, as determined by the presence of either 6p CN-LOH or inactivating mutations in HLA alleles, are shown in blue. Patients with MDS-associated somatic mutations are shown in red. One patient had a transient clone of whole chromosome 6 CN-LOH early in disease course (blue circle accompanied by curved black arrow at the bottom right), which disappeared and was replaced by a dominant clone with MDS-associated mutations (red circle, indicated by a curved black arrow at the bottom right). HLA risk alleles are indicated next to each of the points; A, HLA-A; B, HLA-B.

Babushok, Blood Adv 2017
Acquired Aplastic Anemia

Clonal Hematopoiesis in AA

Fig 1. Clonal hematopoiesis in aplastic anemia. In aplastic anemia (AA), cytotoxic T lymphocyte (CTL)-mediated attack on the hematopoietic stem and progenitor cells (HSPCs) leads to an evolutionary “bottleneck”. Pre-existing age-related genetic mutations (1), depicted as circles of different colors, serve as a substrate for clonal selection. Cells that are either less immunogenic or more resistant to CTL-mediated apoptosis (2) or cytokine-mediated marrow suppression (3) have a relative growth advantage in the setting of autoimmunity, leading to immune escape of mutant HSPCs. During hematopoietic recovery (6), genetic events that increase HSPC replicative potential (depicted by circular arrows) lead to expansion of mutant clones. IST, immunosuppressive therapy.
Acquired Aplastic Anemia in children

What is acquired aplastic anemia?

How A.L.G. acts is unknown, but our findings accord with the hypothesis that, in a substantial proportion of cases of aplastic anaemia, unspecified autoimmune reactions block the development of residual stem cells.

Speck, Lancet 1977
Aquired aplastic Anemia
An immune mediated disease: Clinical evidence

Table 2. Response to Treatment with Antilymphocyte Globulin, Methylprednisolone, and Cyclosporine in Patients Who Could Be Evaluated 3, 6, and 12 Months after Initial Treatment.*

<table>
<thead>
<tr>
<th>Time of Evaluation</th>
<th>Control Group</th>
<th>Cyclosporine Group</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO. OF</td>
<td>% OF TOTAL IN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PATIENTS</td>
<td>REMISSION</td>
<td></td>
</tr>
<tr>
<td>3 Months</td>
<td>41</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>Complete remission</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>11</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>No remission</td>
<td>25</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>20</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>35</td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>Complete remission</td>
<td>6</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>13</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>No remission</td>
<td>22</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>13</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Survival after Antithymocyte Globulin Treatment in 41 Patients with Severe Aplastic Anemia and in 15 with Moderate Aplastic Anemia. Tick marks denote patients alive at the time of the analysis.

Champlin, NEJM 1983

Figure 3. Failure-free survival. Patients treated with CsA (ATG + CsA) had longer failure-free survival times than patients treated without CsA (ATG).

Frickhofen, Blood 2003

Risk of Relapse 38%
PNH/Clonal evolution/malignancy 25%
CSA dependence (CSA Group) 26%

Frickhofen, NEJM 1991
Immunsuppressive Therapy in Children with AA
Excellent OS despite considerable incidence of NR, relapse and clonal evolution

Table V. Paediatric studies of immune suppressive therapy (IST) with horse ATG and ciclosporin.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Treatment (IST)</th>
<th>Study period</th>
<th>Follow up (years)</th>
<th>Overall response</th>
<th>Overall survival</th>
<th>Relapse rate</th>
<th>Clonal evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuhrer et al. (2005)</td>
<td>146</td>
<td>ATG, CSA, GCSF</td>
<td>1993–2001</td>
<td>4-1 (median)</td>
<td>CR 69% VSAA, CR 44% SAA</td>
<td>93% VSAA, 81% SAA</td>
<td>13% VSAA, 14% SAA</td>
<td>NR</td>
</tr>
<tr>
<td>Kamio et al. (2011)</td>
<td>441</td>
<td>ATG, CSA, ±Dan ±GCSF</td>
<td>1992–2007</td>
<td>10</td>
<td>59-9%</td>
<td>82% VSAA, 82% SAA</td>
<td>11.9%</td>
<td>NR</td>
</tr>
<tr>
<td>Saracco et al. (2008)</td>
<td>42</td>
<td>ATG, CSA± GCSF</td>
<td>1991–1999</td>
<td>10</td>
<td>71%</td>
<td>83%</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Scheinberg et al. (2008)</td>
<td>77</td>
<td>ATG, CSA, ±MMF, ±sirolimus</td>
<td>1989–2006</td>
<td>10</td>
<td>77%</td>
<td>80%</td>
<td>33%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

ATG, Anti-Thymocyte Globulin; CSA, ciclosporin; Dan, Danazol; GCSF, granulocyte colony-stimulating factor; MMF, mycophenolate mofetil; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia; NSAA, non severe aplastic anaemia; NR, not reported; CR, Complete remission rate.

Samarasinghe, BJH 2012
Horse versus Rabbit ATG in SAA

hATG is associated with a better response to IST and better survival

Table 2. Hematologic Response at 3 and 6 Months to Horse ATG and Rabbit ATG.

<table>
<thead>
<tr>
<th>Response</th>
<th>Horse ATG (N = 60)</th>
<th>Rabbit ATG (N = 60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>95% CI</td>
<td>no. (%)</td>
</tr>
<tr>
<td>At 3 mo</td>
<td>37 (62)</td>
<td>49–74</td>
<td>20 (33)</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>41 (68)</td>
<td>56–80</td>
<td>22 (37)</td>
</tr>
</tbody>
</table>

Scheinberg, NEJM 2011
Horse versus Rabbit ATG in SAA

hATG is associated with a better response to IST
EWOG-SAA 2010: IST

Response to IST d180: Thymo (n=35) vs ATGAM (n=69)

- **Thymo** (n=35): 29% CR, 71% GPR
- **Atgam** (n=69): 45% CR, 55% GPR

- CR: Complete Remission
- GPR: Good Partial Remission
- PPR: Partial Remission
- NR: No Response
- SCT: Stable Disease
- clon evol: Clonal Evolution
- relapse: Relapse
- death: Death

05.03.2018
Immunosuppressive treatment for aplastic anemia: are we hitting the ceiling?

Jakob R. Passweg and André Tichelli

hATG, CSA and MMF

Table II. Overall response.

<table>
<thead>
<tr>
<th>Time/response</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Total response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>14 (14)</td>
<td>44 (43)</td>
<td>58 (56) 60%</td>
</tr>
<tr>
<td>6 months</td>
<td>16 (16)</td>
<td>48 (46)</td>
<td>64 (62) 61%</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response.

hATG, CSA ± sirolimus

Table 3. Response to the immunosuppressive regimens.

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th></th>
<th>6 months</th>
<th></th>
<th>Total response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR (%)</td>
<td>PR (%)</td>
<td>CR (%)</td>
<td>PR (%)</td>
<td>CR + PR (%)</td>
</tr>
<tr>
<td>h-ATG/CsA</td>
<td>3 (7)</td>
<td>21 (50)</td>
<td>5 (12)</td>
<td>21 (50)</td>
<td>26 (62%)</td>
</tr>
<tr>
<td>h-ATG/CsA/sirolimus</td>
<td>0 (0)</td>
<td>13 (37)</td>
<td>0 (0)</td>
<td>18 (51)</td>
<td>18 (51%)</td>
</tr>
</tbody>
</table>

CI of relapse 35%

Fig 1. Cumulative incidence of relapses (from day 0 to 1500) among responders (solid line) with 95% confidence intervals (dotted lines).
IST in SAA
Predictive Markers for Repsonse to IST

- Disease Severity
- Age
- Pre-treatment reticulocyte count
- Pre-treatment lymphocyte count
- Interval from diagnosis to treatment
- Skewing of the Vß repertoire
- Presence of PNH clone at diagnosis
- Telomere length

- Score of PNH+/TL not shortened

Figure 2. Response rates of immunosuppressive therapy (IST) at 3 and 6 months according to predicting stratification.

No factor with sufficient and reliable prognostic power to allow stratification.

Führer, Blood 2005
Scheinberg, J Pediatrics 2008
Yoshida, Haematologica 2011
Sugimori, Blood 2006
Maciejewski, BJH 2001
Schuster, BJC 2011
Narita, Haematologica 2015
Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

Matthew J. Olnes, M.D., Ph.D., Phillip Scheinberg, M.D., Katherine R. Calvo, M.D., Ronan Desmond, M.D., Yong Tang, M.D., Ph.D., Bogdan Dumitriu, M.D., Ankur R. Parikh, M.D., Susan Soto, B.S.N., Angelique Biancotto, Ph.D., Xingmin Feng, M.D., Ph.D., Jay Lozier, M.D., Ph.D., Colin O. Wu, Ph.D., Neal S. Young, M.D., and Cynthia E. Dunbar, M.D.

Table 1. Baseline Characteristics of the Patients.1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>44</td>
</tr>
<tr>
<td>Range</td>
<td>18–77</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Black</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>14 (54)</td>
</tr>
<tr>
<td>Time since diagnosis — mo</td>
<td>26</td>
</tr>
<tr>
<td>Range</td>
<td>13–138</td>
</tr>
<tr>
<td>Time since last intensive IST — mo</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
</tr>
<tr>
<td>Range</td>
<td>6–117</td>
</tr>
<tr>
<td>Prior courses of intensive IST — no.</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
</tr>
<tr>
<td>Range</td>
<td>1–4</td>
</tr>
<tr>
<td>Response to prior intensive IST — no. (%)‡</td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>23 (88)</td>
</tr>
<tr>
<td>Relapsed refractory</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

Figure 1. Lineage Characteristics of Responses to Eltrombopag.
The Venn diagrams show the numbers of patients with unilineage, bilineage, and trilineage hematologic responses. The numbers of patients with a response and their response pattern at 12 weeks are shown on the left. The numbers of patients who met the response criteria at the most recent follow-up assessment are shown on the right.

NEJM, 2012
Eltrombopag in SAA

Clinical Trials

Eltrombopag Added to Standard Immunosuppression in Treatment-Naive Severe Aplastic Anemia (NCT01623167)
Sponsor: NIH
Phase 1/2 study to test the safety and effectiveness of adding eltrombopag to standard immunosuppressive therapy for severe aplastic anemia.
# Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

<table>
<thead>
<tr>
<th>Cohort and Response</th>
<th>Rate at 3 Mo</th>
<th>Rate at 6 Mo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Response — no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td>23 (77 [61–93])</td>
<td>24 (80 [65–95])</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>18 (60 [41–79])</td>
<td>14 (47 [28–66])</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>5 (17 [3–31])</td>
<td>10 (33 [15–31])</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Response — no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td>24 (77 [62–93])</td>
<td>27 (87 [75–100])</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (52 [33–70])</td>
<td>19 (61 [43–79])</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>8 (26 [9–42])</td>
<td>8 (26 [9–42])</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Cohort 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Response — no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td>27 (87 [75–100])</td>
<td>29 (94 [84–103])</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>12 (39 [21–57])</td>
<td>11 (35 [18–53])</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>15 (48 [30–67])</td>
<td>18 (58 [40–76])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>All cohorts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>92</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Response — no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td>74 (80 [72–89])</td>
<td>80 (87 [80–94])</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Partial response</td>
<td>46 (50 [40–60])</td>
<td>44 (48 [37–58])</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>28 (30 [21–40])</td>
<td>36 (39 [29–49])</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Eltrombopag in SAA

Clinical Trials

Eltrombopag Added to Standard Immunosuppression in Treatment-Naive Severe Aplastic Anemia (NCT01623167)
Sponsor: NIH
Phase 1/2 study to test the safety and effectiveness of adding eltrombopag to standard immunosuppressive therapy for severe aplastic anemia.

RACE: hATG+CsA vs hATG+CsA+Eltrombopag for SAA
Sponsor: EBMT
A Prospective Randomized Multicenter Study Comparing Horse Antithymocyte Globuline (hATG) + Cyclosporine A (CsA) With or Without Eltrombopag as Front-line Therapy for Severe Aplastic Anemia Patients

Eltrombopag in addition to standard IST (CETB115E2201)
Sponsor: Novartis
A phase II, open-label, non-controlled, intra-patient dose-escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in refractory, relapsed/recurrent or treatment naïve pediatric patients with severe aplastic anemia
Acquired Aplastic Anemia

Traditional Treatment Algorithm for Children and Adolescents

SAA

MRD ?

yes

HSCT

no

IST

ATG/CSA+/-G-CSF

NR

HSCT
Acquired Aplastic Anemia in Children

Overall Survival following MSD-HSCT and IST

**SAA94**

![Probability of overall survival according to the year of HSCT.](Image)

Fig. 3: Probability of overall survival according to the year of HSCT.

<table>
<thead>
<tr>
<th>Med. age at Dx:</th>
<th>10.4 (1.9-16.5) years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity:</td>
<td>VSAA 53, SAA 29, NSAA 6</td>
</tr>
<tr>
<td>Prep. Regimen:</td>
<td>Cy/ATG</td>
</tr>
<tr>
<td>GvHD Prophylaxis:</td>
<td>CSA/MTX</td>
</tr>
</tbody>
</table>

N=213

<table>
<thead>
<tr>
<th>Med. age at Dx:</th>
<th>10 (0-16) years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prep. Regimen:</td>
<td>Cy+-ATG+-TBI, Flu/Cy+-ATG+-TBI</td>
</tr>
<tr>
<td>GvHD Prophylaxis:</td>
<td>CSA/MTX (174)</td>
</tr>
</tbody>
</table>

Strahm, BMT, EBMT abstract 2013

Yoshida, Haematologica 2014
## MUD-HSCT

### Review of major series involving UD Allo-HSCT

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Allo-HSCT period</th>
<th>OS</th>
<th>Impact of age</th>
<th>Impact of time from diagnosis to Allo-HSCT</th>
<th>Impact of HLA matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deeg et al.</td>
<td>50</td>
<td>1994-1999</td>
<td>58%</td>
<td>20 years</td>
<td>1 year and 3 years</td>
<td>No</td>
</tr>
<tr>
<td>Kojima et al.</td>
<td>154</td>
<td>1993-2000</td>
<td>56%</td>
<td>20 years</td>
<td>1 year and 3 years</td>
<td>Yes</td>
</tr>
<tr>
<td>Bacigalupo et al.</td>
<td>87</td>
<td>1998-2004, 2005-2008</td>
<td>68%</td>
<td>13 years</td>
<td>2 years</td>
<td>No</td>
</tr>
<tr>
<td>Marsh et al.</td>
<td>29</td>
<td>1999-2009</td>
<td>83%</td>
<td>*</td>
<td>*</td>
<td>N/A</td>
</tr>
<tr>
<td>Maury et al.</td>
<td>37</td>
<td>1989-1999</td>
<td>29%</td>
<td>17 years</td>
<td>1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Viollier et al.</td>
<td>35</td>
<td>1990-1997</td>
<td>32%</td>
<td>*</td>
<td>*</td>
<td>Yes</td>
</tr>
<tr>
<td>Devillier et al.</td>
<td>46</td>
<td>2000-2005</td>
<td>52%</td>
<td>30 years</td>
<td>1 year</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant

Fig 2. (A) Probability of 3-year OS (Kaplan–Meier method) for the whole population of 537 patients stratified by treatment. Front-line IST: patients receiving IST upfront, excluding those who were subsequently transplanted. Subgroup analysis: First-line MFD HSCT vs. Front-line IST: $P = 0.21$. First-line MFD HSCT vs. HSCT post-failed IST: $P = 0.02$. Front-line IST vs. HSCT post-IST failure: $P = 0.047$. (B)
EWOG-SAA 2010

Stratification of therapy according to donor availability

SAA

MRD ?

yes -> HSCT

no -> IST

ATG/CSA+/G-CSF

NR

HSCT

MUD

MRD ?

yes -> MUD

no -> HSCT

NR

HSCT
Upfront unrelated HSCT in children with SAA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median FUP</th>
<th>Upfront MUD/MMUD HSCT (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median age at HSCT (range), years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethnicity (Caucasian:Other) (n=26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median year of HSCT (range)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median interval between diagnosis and HSCT (range), months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stem cell source: Bone marrow/PBSC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median CD34 cell dose (x10^6/kg) (n=23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median In-patient hospital stay (range), days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time to neutrophil recovery (&gt;0.5x10^9/l), days (range)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time to platelet recovery (&gt;50x10^9/l), days (range)</td>
</tr>
</tbody>
</table>

Outcome:
- Median FUP: 22 months
- pOS at 2.5 yrs: 95%
- pEFS at 2.5 yrs: 92%
- Donor chimerism, median(range): 100 (88-100)%
- aGvHD °III-IV: 7.4%
- cGvHD: 22.2% (limited to skin)

Bathnagar, BMT – EBMT abstract 2014
Acquired Aplastic Anemia in children

Summary and future challenges

- AA is an acquired immune-mediated disease
- Exclusion of IBMF and other differential diagnosis is essential
- Diagnostic tools must be clinically meaningful and should not delay treatment
  - Teleomere length
  - Screening for germline and/or somatic mutations
- Immunosuppressive therapy remains a valuable treatment option
  - no improvement by intensified IS
  - no valuable biomarker for stratification available → TL/PNH?
  - addition of eltrombopag should be studied within clinical trials
- HSCT offers excellent outcome
  - MSD-HSCT is considered standard of care
  - MUD-HSCT is considered standard of care after IST failure
  - role of upfront MUD HSCT should be studied in clinical trials
The EWOG-Community

Members
Pediatric Hem/Onc Societies of 18 Nations
Organized by
Regional Coordinators, Pathologists, Cytogeneticists

Austria
Czech Republic
Germany
Hungary
Israel
Ireland
Poland
Spain
Switzerland
Belgium
Denmark
Greece
Island
Italy
Norway
Slovakia
Sweden
The Netherlands
Acquired Aplastic Anemia

- An immune-mediated disease: destruction of HSPC