Treatment for acquired severe aplastic anaemia (SAA) in childhood

Gergely Kriván
Overview

• Aplastic anemia (AA) is a rare disease characterized by pancytopenia and aplasia of hematopoietic stem cells

  - Idiopathic acquired AA is thought to result from an activated T-lymphocyte-mediated destruction of hematopoietic stem cells

• AA could be mistaken for RCC, the most common form of myelodysplastic syndrome (MDS) in childhood (81% of RCC pts characterized by hypocellular bone marrow)

• In contrast to MDS, blood cells in patients with AA generally function normally and do not contain chromosomal abnormalities

• AA may develop into clonal disorders including MDS, paroxysmal nocturnal hemoglobinuria (PNH), and acute myelogenous leukemia (AML)

AA and other bone marrow failure syndromes

SDS, Shwachman-Diamond syndrome; DKC, dyskeratosis congenita; LGL, large granular lymphocyte

Epidemiology

- Rare; incidence is ~2-3/million per year in Europe and North America; affecting 300-600 people in US each year
- Acquired AA is more common in developing countries
  - 2x-3x more common in Asia than in Western countries
- AA is most commonly diagnosed in children and young adults or people older than 60 years
  - with a peak incidence between 15-25 y

Age and gender distribution of SAA

Median ~24 y/o

Age cohort

Number

Female
Male

Neil S. Young, 2006
## Causes of Aplastic Anemia

### Acquired (~80%)

- **Idiopathic factors**
- Infectious diseases: hepatitis (5-10%), EBV, HIV, parvovirus, mycobacteria
- Toxic exposure to radiation and chemicals such as benzene
- Drugs/elements: chloramphenicol, phenylbutazone, gold, anti-epileptics, chemotherapy
- Paroxysmal nocturnal haemoglobinuria (PNH)
- Transfusional GvHD
- Pregnancy
- Eosinophilic fasciitis

### Congenital or inherited (~20%)

- Fanconi anemia
- Dyskeratosis congenita (DKC)
- Cartilage-hair hypoplasia
- Pearson syndrome
- Congenital amegakaryocytic thrombocytopenia (CAMT)
- Shwachman-Diamond syndrome
- Dubowitz syndrome
- Diamond-Blackfan syndrome
- Familial aplastic anemia

# Classification of AA

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| Non-severe (or mild)  | • Hypoplastic bone marrow<br>
|                       | • Low blood counts, but not severe enough for SAA                           |
| Severe                | • Hypoplastic bone marrow (<25% or 25%-50% with <30% residual hemopoietic cells) with 2 of the following<br>
|                       | • Platelet count <20 x 10⁹/L<br>
|                       | • Reticulocyte count <20 x 10⁹/L<br>
|                       | • Neutrophil count <0.5 x 10⁹/L                                             |
| Very severe*          | • Hypoplastic bone marrow as above for severe AA with<br>
|                       | • Neutrophil count <0.2 x 10⁹/L                                             |

*Predominant in children (>60%)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical history</td>
<td>Recent illness/hepatitis; drug/toxin exposure; family history of malignancy, congenital abnormalities, blood disorders, consanguinity</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Assess for congenital abnormalities, vital signs, height/weight</td>
</tr>
<tr>
<td>Blood counts</td>
<td>Full blood count and reticulocyte count, blood film</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Liver function tests, vitamin B12 and folate, HbF% (pre-transfusion)</td>
</tr>
<tr>
<td>Blood group, antibody screen</td>
<td></td>
</tr>
<tr>
<td>BM biopsy</td>
<td>Careful evaluation by an experienced hematopathologist to rule out hypoplastic RCC</td>
</tr>
<tr>
<td>BM cytogenetics</td>
<td>Including FISH for chromosome 5 and 7 if any MDS features present</td>
</tr>
<tr>
<td>Viral serology</td>
<td>Hepatitis A, B, C, CMV, EBV, pervovirus B19, VZV, measles, HSV, HHV6, HIV, adenovirus</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>CD55-59 for PNH</td>
</tr>
<tr>
<td>Immunology</td>
<td>Lymphocyte subsets, Ig-s, and autoantibody screen</td>
</tr>
<tr>
<td>HLA typing</td>
<td>If no matched family donor, perform MUD donor search</td>
</tr>
<tr>
<td>Imaging</td>
<td>Chest X ray, abdominal/cardiac US</td>
</tr>
<tr>
<td>DEB or mitomycin induced chromosomal breakage test</td>
<td>Rule out Fanconi</td>
</tr>
<tr>
<td>Other</td>
<td>FISH for telomere length in DKC, pancreatic functions in SDS etc., molecular genetics for TERC, TERT etc. for telomere shortening</td>
</tr>
</tbody>
</table>

Modified from Samarasinghe S. Br J Haematol. 2012;157:43-70
BM histology in SAA
Factors influencing treatment decisions in pts. with acquired AA

- Severity of disease (scoring system based on BM cellularity, plt, neutrophil and reticulocyte counts)
- Patient’s age (< 20y)
- Availability of HLA identical family donor
Response criteria in SAA

- Partly depend on pre-treatment disease severity
- **Complete response (CR):** normalization of blood counts
  - Neutrophil count $\geq 1.5 \text{ G/l}$
  - Platelet count $\geq 150 \text{ G/l}$
  - Hemoglobin $\geq 120 \text{ g/l}$
- **Partial response (PR)**
  - Transfusion independency
  - Improvement of the disease severity
    - or
    - Neutrophil count $\geq 0.5 \text{ G/l}$
    - Platelet count $\geq 20 \text{ G/l}$
    - In case of counts were lower before treatment
- **No response**
  - Persistent transfusion need
  - or lower values than above mentioned
Initial therapeutic choice in children with SAA

- **HLA identical sibling donor**
  - Yes: Allogeneic hematopoietic stem cell transplantation (HSCT)
  - No: Immunosuppressive treatment (IST)
Trials comparing OS following SCT and IST in children

<table>
<thead>
<tr>
<th>Study</th>
<th>SCT</th>
<th>IST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>2-6 y OS (%)</td>
</tr>
<tr>
<td>Lawlor, 1997</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>Gillio, 1997</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td>Führer, 1998</td>
<td>26</td>
<td>84</td>
</tr>
<tr>
<td>Pitcher, 1999</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>Kojima, 2000</td>
<td>37</td>
<td>97</td>
</tr>
<tr>
<td>Fouladi, 2000</td>
<td>26</td>
<td>93</td>
</tr>
</tbody>
</table>
Submissions for HSCT in Hungary in children

<table>
<thead>
<tr>
<th>Year</th>
<th>Autologus</th>
<th>Allogeneic</th>
<th>MUD search needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>33</td>
<td>46</td>
<td>26 (56%)</td>
</tr>
<tr>
<td>2006</td>
<td>20</td>
<td>29</td>
<td>19 (66%)</td>
</tr>
<tr>
<td>2008</td>
<td>36</td>
<td>41</td>
<td>29 (71%)</td>
</tr>
<tr>
<td>2010</td>
<td>35</td>
<td>42</td>
<td>38 (90%)</td>
</tr>
</tbody>
</table>
Important conclusions from IST studies

- **ATG + CSA** most effective IST combination; addition of **CSA** to **ATG** improves response rates (OR 65% vs. 31% at 6 months) but not overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts.</th>
<th>Median age, (y)</th>
<th>IST regimen</th>
<th>Response at 6 mo (%)</th>
<th>Relapse (%)</th>
<th>Clonal evolution(%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacigalupo 2000</td>
<td>100</td>
<td>16 (1-72)</td>
<td>ALG, CSA, MP, G-CSF</td>
<td>77% (CR+PR)</td>
<td>9%</td>
<td>8%</td>
<td>87% (5y)  76% (ANC&lt;0,2) 98% (ANC&gt;0,2)</td>
</tr>
<tr>
<td>Kojima 2000</td>
<td>119</td>
<td>9 (1-18)</td>
<td>hATG, CSA Danazol +/-G-CSF</td>
<td>55-77% (CR+PR)</td>
<td>22%</td>
<td>6% (3y)</td>
<td>88% (3 y)</td>
</tr>
<tr>
<td>Führer 2005</td>
<td>146</td>
<td>9 (1-17)</td>
<td>(h)ATG, CSA, G-CSF</td>
<td>44% CR (SAA) 69% CR (vSAA)</td>
<td>NR</td>
<td>NR</td>
<td>81% (5y, SAA) 93% (5y, vSAA)</td>
</tr>
<tr>
<td>Saracco 2008</td>
<td>42</td>
<td>9 (1-20)</td>
<td>hATG, CSA +/-G-CSF</td>
<td>71% (CR+PR)</td>
<td>16% (10y)</td>
<td>15% (10y)</td>
<td>83% (10y)</td>
</tr>
<tr>
<td>Pongtanakul 2008</td>
<td>42</td>
<td>8,5 (1,4-17,3)</td>
<td>(h)ATG, CSA, MP +/- G-CSF</td>
<td>62% CR 19% PR</td>
<td>5%</td>
<td>5%</td>
<td>67,5% (5y)</td>
</tr>
<tr>
<td>Scheinberg 2008</td>
<td>77</td>
<td></td>
<td>hATG, CSA +/-MMF ± sirolimus</td>
<td>77% (CR+PR)</td>
<td>33% (10y)</td>
<td>8,5% (10y)</td>
<td>80% (10y)</td>
</tr>
<tr>
<td>Kamio 2011</td>
<td>441</td>
<td>8,3 (0-17)</td>
<td>hATG, CSA +/-Danazol +/-G-CSF</td>
<td>59,9%</td>
<td>11,9% (10y)</td>
<td>NR</td>
<td>82% (10y, SAA) 82% (10y, vSAA) 98% (10y, nSAA)</td>
</tr>
</tbody>
</table>
Predictors of response after IST

Survival rate after IST for children with vSAA (93% after 5 years; 95% CI, 88%-98%) and SAA (81% after 5 years; 95% CI, 69%-93%; P < .001).

Predictors of response after IST

Summary - IST

• Most frequently employed approach

• Response rates (RR): 60-80%
  - Favorable predictors: younger age, high pre-treatment reticulocyte and lymphocyte count, male gender, shorter interval Dx-Rx, leukocyte count < 2 G/l

• Long term events (at 10 years):
  - Relapses: 10-33 %
  - Adverse predictors: partial remission, fast CsA tapering (?)
  - Evolution to clonal diseases: 10-15%
  - Long term OS: 80-90%

IST - Questions to be answered (1)

- **Combinations/alternatives in IST:** no advantage yet

- **G-CSF:** no advantage for OS/EFS; predicts response; increase the risk of clonal disorders

- **Cyclosporin tapering:** late (>12 m) and slow (0.25-0.5 mg/kg/m) or no effect?
IST - Questions to be answered (2)

- **Steroids for serum sickness prevention?**
  - How long and what dose?

- **Telomer shortening in SAA**: 5-10% in SAA; no effect on response rate, but adversely affects relapse rate, clonal evolution and survival

- **Horse or Rabbit ATG**: horse
  - Overall response (6m) 68% vs. 37%, OS (3y): 96% vs 76%
  - Overall response (6m) 59,5% vs. 334,5%, OS (2y): 78,4% vs 55,4%
## ATG products studied in aplastic anemia

<table>
<thead>
<tr>
<th>Generic/Brand names</th>
<th>Animal source</th>
<th>Cell source</th>
<th>Dosing</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithymocyte globulin (equine)/Atgam</td>
<td>Horse</td>
<td>Human thymus lymphocytes</td>
<td>40 mg/kg iv. daily x 4 days</td>
<td>North America, Asia, Africa, South America</td>
</tr>
<tr>
<td>Antithymocyte globulin (equine)/Lymphoglobulin(e)</td>
<td>Horse</td>
<td>Human thymus lymphocytes</td>
<td>15 mg/kg iv. daily x 5 days</td>
<td>No longer available</td>
</tr>
<tr>
<td>Antithymocyte globulin (rabbit)/Thymoglobulin(e)</td>
<td>Rabbit</td>
<td>Human thymus lymphocytes</td>
<td>2.5-3.75 mg/kg iv. daily x 5 days</td>
<td>North America, Europe, Asia, Africa, South America</td>
</tr>
<tr>
<td>Antithymocyte globulin (rabbit)/ATG-Fresenius</td>
<td>Rabbit</td>
<td>Human T-lymphoblasts from Jurkat cell line</td>
<td>5 mg/kg iv. daily x 5 days</td>
<td>Europe, Asia</td>
</tr>
</tbody>
</table>
IST - Questions to be answered (2)

• Steroids for serum sickness prevention?
  • How long and what dose?

• **Telomer shortening in SAA:** 5-10% in SAA; no effect on response rate, but adversely affects relapse rate, clonal evolution and survival
  • Scheinberg P et al. Association of telomere length of peripheral blood leukocytes with hematopoietic relapse, malignant transformation, and survival in severe aplastic anemia. JAMA 2010:304(12):1358-64.

• **Horse or Rabbit ATG:** horse
  • Overall response (6m) 68% vs. 37%, OS (3y): 96% vs 76%
  • Scheinberg P et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med 2011: 365:348-354. *(20 vs 30% of pts were children)*
  • Overall response (6m) 59,5% vs. 334,5%, OS (2y): 78,4% vs 55,4%
Horse vs rabbit
(from the EBMT SAA Working Party)

A
Overall survival for all patients
Horse ATG; n=105
Rabbit ATG; n=35

Surviving

1,000
0,750
0,500
0,250
0

0,0
133,3
266,7
400,0
533,3
666,7
800,0
days from ATG

86%
68%
P=0.009

B
Transplant free survival for all patients: transplant is considered an event
h-ATG
r-ATG

Surviving

1,000
0,750
0,500
0,250
0

0,0
133,3
266,7
400,0
533,3
666,7
800,0
days from ATG

76%
52%
P=0.002

C
Overall survival for severe aplastic anemia
Horse ATG; n=67
Rabbit ATG; n=26

Surviving

1,000
0,750
0,500
0,250
0

0,0
200,0
400,0
600,0
800,0
days from ATG

91%
73%
P=0.01

D
Transplant free survival for severe aplastic anemia: transplant is considered an event
Horse ATG; n=67
Rabbit ATG; n=26

Surviving

1,000
0,750
0,500
0,250
0

0,0
200,0
400,0
600,0
800,0
days from ATG

80%
64%
P=0.04


105 horse vs 35 rabbit pts (36y 17-75y)
Horse vs rabbit
(from Germany/Austria/Switzerland)

A
Transplant free survival

B
Overall survival

Pts: all children

IST - Questions to be answered (3)

- **Second course of IST**: could be helpful, but MUD HSCT is better - FFS (5y) 83,9% vs. 9,5%

- Kosaka et al. Prospective multicenter trial comparing repeated immunosuppressive therapy with stem cell transplantation from an alternative donor as second line treatment for children with severe and very severe aplastic anemia. Blood. 2008: 11:1054-59

- OR after second course: 60-70%


Factors contributing to results of MSD-HSCT in children (1)

- **OS: 85-100%**

- **Improved transplant technology, supportive care and anti-infective management**
Factors contributing to results of MSD-HSCT in children (2)

• **Graft rejection rate:** 5%
  - Risk factors:
    • preceding immunosuppressive therapy with ATG+CSA (Kobayashi, 2006)
    • low marrow cell dose (Niederwieser 1988)
    • recipient/donor gender mismatching - F/M (Stern 2006)
    • progressive mixed chimerism (McCann, 2007)
  - Prevention
    • early transplantation (< 1 months after dg)
    • modest transfusion burden (leucocyte depleted blood products, platelets collected by apheresis)
    • serial chimerism monitoring
    • addition of ATG to cyclophosphamide

• **Acute GvHD:** 10-20%
  - use of CSA-MTX prophylaxis (Bacigalupo, 2000; Locatelli, 2000)
  - no donor buffy coat or TAI against rejection (Ades, 2004)
Relationship of acute GvHD and OS

Akut GvHD utáni túlélés (Kaplan-Meier)

Meghalt  +  Túlélő

No aGvHD: 93%
Acute GvHD: 37%
p=0.015

N=27 pts
Factors contributing to results of MSD-HSCT in children (3)

- **Chronic GvHD**: 10-30%
  - Risk factors
    - previous acute GvHD (Storb, 1983)
    - full donor chimerism (McCann, 2007)
    - high nucleated marrow cell dose ($\geq 3.4 \times 10^8$/kg) (Kahl, 2005)
    - use of PB cells (Eapen 2011)
  - Prevention
    - more BM and less PBSC donation (Schrezenmeier, 2003)
    - alemtuzumab containing regimen (Marsh 2011)

- **Late consequences**: infertility, malignancy (7-13%)
  (Kahl, 2005, Sanders 2011)
  - Prevention
    - conditioning without irradiation (Bacigalupo, 2000; Ades, 2004)
    - prevention of cGvH
Recommended regimen for MSD-HSCT in children

- **Conditioning regimen**: Cy 50mg/kg x 4 days
  ± ATG (rabbit 2.5 mg/kg x 3-4; horse 30mg/kg x 5) or alemtuzumab (0.9-1 mg/kg)

- **GvH prophylaxis**: MTX 10 mg/m² on days +1, +3 and +6 and CSA 3 mg/kg iv (6 mg/kg p os) for at least 9 months
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts.</th>
<th>Donor source</th>
<th>Cond.</th>
<th>Age (y)</th>
<th>aGvH (%)</th>
<th>cGvH (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kojima 2001</td>
<td>15</td>
<td>MUD: 11</td>
<td>Cy-ATG-TBI</td>
<td>11</td>
<td>33</td>
<td>13</td>
<td>100 at 4y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMUD: 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vassiliou 2001</td>
<td>8</td>
<td>MUD: 7</td>
<td>Cy-CP-TBI</td>
<td>7</td>
<td>25</td>
<td>0</td>
<td>100 at 3y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMUD: 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Benesch 2004</td>
<td>9</td>
<td>MUD: 4</td>
<td>↑ CD34&lt;sup&gt;+&lt;/sup&gt; dose, TCD, CY-ATG-TLI or TBI±TT</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>89 at 4y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMUD: 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kang 2004</td>
<td>5</td>
<td>MUD</td>
<td>Cy-Flu-ATG</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>80 at 2y</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacigalupo 2005</td>
<td>38</td>
<td>MUD: 33</td>
<td>Cy-Flu-ATG</td>
<td>14</td>
<td>11</td>
<td>27</td>
<td>73 at 2y</td>
</tr>
<tr>
<td></td>
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<td>MMRD: 5</td>
<td></td>
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<tr>
<td>Bunin 2006</td>
<td>12</td>
<td>MUD: 4</td>
<td>Partial TCD, TBI+ CY-AraC or Cy-TT or ATG</td>
<td>9</td>
<td>33</td>
<td>25</td>
<td>75 at 4y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMUD: 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez-Albuernre 2008</td>
<td>195</td>
<td>MUD: 129</td>
<td>Various</td>
<td>&lt;5y: 30</td>
<td>43</td>
<td>35</td>
<td>51 at 5y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMUD: 66</td>
<td></td>
<td>5-10y: 58</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>&gt;10-21y: 107</td>
<td></td>
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</tr>
<tr>
<td>Samarasinghe 2012</td>
<td>44</td>
<td>MUD</td>
<td>Flu-Cy-Alemtuzumab</td>
<td>8,1</td>
<td>34,1</td>
<td>6,8</td>
<td>95,1% at 5y</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(3,8-19)</td>
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</tbody>
</table>
Factors contributing to results of MUD-HSCT in children

- Similar factors like for MSD-HSCT
- Recipient age (Bacigalupo, 2005; Locasiulli, 2007; Perez-Albuerne, 2008)
- Length of time from diagnosis (Deeg, 1999; Locasiulli, 2007; Perez-Albuerne, 2008)
- Improved HLA match (Viollier, 2008; Perez-Albuerne, 2008)
  - Extended donor registries
  - Refined, high resolution HLA typing
- Improved conditioning regimens (different approaches)
  - Fludarabine-based (Bacigalupo, 2010)
  - T cell depletion (anti CD3/CD19) or CD34+ selection
Recommended regimen for MUD HSCT in children

- No generally accepted recommendations
- EBMT recommendation (Bacigalupo, 2005)

**Conditioning regimen (1):** Cy 300 mg/m² x4, fludarabine 30 mg/m² x4, rATG 7.5 mg/kg, but: ↑graft failure rate (32% if ≥ 15 years), PTLD and GvHD (Bacigalupo, 2010)

**Conditioning regimen (2):** in pts ≤ 14y and not sensitized: fludarabine 120 mg/m², Cy 120 mg/kg, rATG 7.5 mg/kg + prophylactic rituximab (against PTLD); if pts≥ 15y or sensitized + 2 Gy TBI (Kojima et al., 2011)

**Conditioning regimen (3):** fludarabine 30 mg/m² x5days, Cy 50 mg/kg x4, ATG (horse 30 mg/kg/d or rabbit 2.5 mg/kg/d) x4 (Korthof et al, SAA-WP EBMT, 2013)

**Conditioning (FCC) regimen (UK) (4):** fludarabine 150mg/m2 + Cy 120mg/kg + Alemtuzumab 0.9 mg/kg; OS/FFS: 95%, aGvH III-IV: 2.3%, cGvH: 6.8% (Samarasinghe, 2012)

- **Stem cell source:** unmanipulated BM graft (10/10 or 9/10 match)
- **GvHD prophylaxis:** CSA+/MTX (no MTX if alemtuzumab)
Further therapeutic decision in children with SAA

HLA identical sibling donor

Yes
Allogeneic HSCT

No
Immunosuppressive treatment (IST) with horse ATG

Response

Yes
Maintain on CSA then very slow taper

No
MUD donor

No MUD donor
2\textsuperscript{nd} rATG+CSA or MMUD (9/10)

10/10 MUD HSCT

10/10 MUD
# Alternative transplants


<table>
<thead>
<tr>
<th>No. Patients</th>
<th>71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participating centres</td>
<td>32</td>
</tr>
<tr>
<td>Age median (y)</td>
<td>13 (2-68)</td>
</tr>
<tr>
<td>Age (&lt;18y) n(%)</td>
<td>43 (61%)</td>
</tr>
<tr>
<td>Median FU (months)</td>
<td>35 (8-83)</td>
</tr>
<tr>
<td>Previous IST</td>
<td>55</td>
</tr>
<tr>
<td>Time (Dg-Tx)</td>
<td>14 (2-140 months)</td>
</tr>
<tr>
<td>&gt;20 RBC</td>
<td>35 (56%)</td>
</tr>
<tr>
<td>&gt; 20 plt transfusions</td>
<td>42 (67%)</td>
</tr>
<tr>
<td>Grafts</td>
<td>1 CBU: 57; 2CBU: 14</td>
</tr>
<tr>
<td>Conditionings</td>
<td>20 regimens</td>
</tr>
<tr>
<td>OS (3y)</td>
<td>38%</td>
</tr>
</tbody>
</table>

NC dose > 4x10^7/kg!  *Peffault de Latour et al: BBMT 2010  


<table>
<thead>
<tr>
<th>No. Patients</th>
<th>73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participating centres</td>
<td>48</td>
</tr>
<tr>
<td>Age median (y)</td>
<td>12 (2,5-70)</td>
</tr>
<tr>
<td>Median FU (months)</td>
<td>33</td>
</tr>
<tr>
<td>Haplo as 1. option</td>
<td>59</td>
</tr>
<tr>
<td>Time (Dg-Tx)</td>
<td>10.5 (0-179)</td>
</tr>
<tr>
<td>Engraftment (median)</td>
<td>58% (3-45 days)</td>
</tr>
<tr>
<td>Acute GvHD</td>
<td>27%</td>
</tr>
<tr>
<td>Chronic GvHD</td>
<td>25%</td>
</tr>
<tr>
<td>OS (3y)</td>
<td>37%</td>
</tr>
<tr>
<td>OS (≥ 3 haplo vs &lt;3 haplo centres)</td>
<td>58 vs 30% (p=0.06)</td>
</tr>
</tbody>
</table>

Supportive care

• Transfusion policy
  - Leukodepleted, irradiated products (CMV?)
  - Restrictive
    • RBC transfusions
      - Anemia with hypoxia
      - Based on symptoms and co-morbidities, QoL issues
    • Plt transfusions if
      - Plt count < (5)-10 G/l
      - Plt count < 20 G/l in the presence of fever, infection
      - Plt count < 50 during ATG treatment

• Chelation: if se ferritin > 1000 ug/L
  - Desferrioxamine or deferasirox (avoid deferiprone)
Overall survival

01.01.1992 - 31.08.2011.

No. of patients: 43

79,1%

Follow up (median): 4,65 y
(0,04-19,24 y)
Survival according to donor type


MRD: 85,7% (n=28)
Alternative: 66,7 % (n=15)

p=0,07 (NS)
Survival according to time of Txp

OS: 68.4% (n=19)

OS: 87.5% (n=24)

$p=0.068$ (NS)