MUD HSCT as first line Treatment in Idiopathic SAA

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No Financial Disclosures
Guidelines for management of aplastic anaemia

Age of patient

≤ 40 years

HLA identical sibling

Yes

HLA id sib BMT

No

ATG + CSA

Response at 4 months

Yes

Options:
1. 3rd ATG if previous response to ATG
2. Oxymetholone
3. CRP using novel IST
4. BMT using CRP with UCB or haploid identical donor?

No

Consider MUD BMT if ≤ 50 years (or 50–60* and good performance status)

2nd ATG + CSA if no MUD

Response at 4 months

Yes

Supportive therapy

No
Fig 1. Treatment of acquired severe aplastic anaemia. HSCT may be considered, using a matched sibling donor or a suitably matched unrelated donor if no matched sibling donor is available, for patients aged 35–50 or >50 years who fail to respond to first line immunosuppressive therapy (Sureda et al, 2015). ATG, antithymocyte globulin; HLA, human leukocyte antigen; HSCT, haemopoietic stem cell transplantation; CSA, ciclosporin.

EBMT SAAWP, Sureda et al, 2015

Fig 2. Treatment of adult refractory severe aplastic anaemia. ATG, antithymocyte globulin; CSA, ciclosporin; HSCT, haemopoietic stem cell transplantation; IST, immunosuppressive therapy. Modified from Marsh, J.C. & Kulasekaran, A.G. 2013.
Primary Treatment of Acquired Aplastic Anemia: Outcomes with Bone Marrow Transplantation and Immunosuppressive Therapy.
Doney, Kristine; Leisenring, Wendy; Storb, Rainer; Appelbaum, Frederick

Study between 1978-1991- HLA identical HSCT had superior survival compared to IST (P<0.001)
Long Term Follow up of MSD HSCT post SAA

A

Percent Survival

Years from Transplant

Aquired AA
Fanconi's Anemia
Censored

B

Percent Survival

Years from Transplant

No Prior cGVHD
Prior cGVHD
Censored

Sanders Blood
2011
Clonal Evolution after IST

Socie 1993 NEJM
Long Term Data Confirms Superiority of MFD HSCT Compared to IST in Children

Dufour et al BJH 2015

Events: Relapse, no response, need for transplant clonal events
MFD BMT HSCT as First Line Treatment- Superior FFS

Table 4. Multivariate analysis of favorable factors for survival in all 599 patients with SAA

<table>
<thead>
<tr>
<th>OS</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment: BMT</td>
<td>1.619</td>
<td>0.881-2.977</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment period: 2000-2009</td>
<td>1.536</td>
<td>0.556-2.753</td>
<td>NS</td>
</tr>
<tr>
<td>Age: &lt;10 years</td>
<td>2.207</td>
<td>1.240-3.927</td>
<td>0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FFS</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment: BMT</td>
<td>4.497</td>
<td>2.935-6.891</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment period: 2000-2009</td>
<td>1.090</td>
<td>0.812-1.464</td>
<td>NS</td>
</tr>
<tr>
<td>Age: &lt;10 years</td>
<td>1.113</td>
<td>0.833-1.488</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMT indicates bone marrow transplantation; NS, not significant.
### Paediatric IST Studies

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, 98% NSAA</td>
<td>11.9%</td>
<td>NR</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.
Eltrombopag improves OR and CR Rates compared to IST historical Controls

1) Clonal Evolution in 7 patients - 4 with monosomy 7.
2) No Increase in BM fibrosis
3) Median Follow up 15 months

<table>
<thead>
<tr>
<th>Table. Hematologic Response</th>
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<tr>
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<td></td>
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<tr>
<td>All Cohorts (n=88)</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>Cohort 1 (n=30)</td>
</tr>
<tr>
<td>EPAG d14 – 6 mos</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>Cohort 2 (n=31)</td>
</tr>
<tr>
<td>EPAG d14 – 3 mos</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>Cohort 3 (n=27)</td>
</tr>
<tr>
<td>EPAG d1 – 6mos</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
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*Evaluable as of 10/29/2015
Overall response (OR) = blood counts no longer meeting criteria for SAA
Partial response (PR) = blood counts not meeting criteria for SAA or CR
Complete response (CR) = ANC ≥ 1,000/µl, hemoglobin ≥ 10 gm/dL, and platelets ≥ 100,000/µl.

Young ASH Abstracts 2015
Absence of PNH Clone and Short Telomere Lengths Predict Response to IST

Kojima 2015
Figure 2. Actuarial probability of failure-free survival after second-line treatments with immunosuppressive therapy (n = 21) or stem-cell transplantation from an alternative donor (n = 31). FFS is defined as survival with response. Death, nonresponse by 6 months, disease progression requiring a second-line therapies, and relapse were considered as treatment failure.
Improvement over last decade with MUD HSCT- EBMT analysis

Survival (%)

Days from transplant

After 2004; n=45
83%

In or before 2004; n=55
68%

P=0.06

Bacigalupo 2010
Haematologica
FCC in Adult SAA- Low Rates of Chronic GVHD

- Marsh et al. Flu 120 mg/kg, cyclo 40 mg/kg and Alemtuzumab. (Graft Failure 9.5 %, acute GVHD 13.7 %, chronic GVHD 4 %)

Marsh et al Blood 2011
Excellent Survival with MUD HSCT following IST Failure

Flu 150mg/m² + Cy 120mg/kg + Alemtuzumab 0.9 mg/kg
95% 5 yr FFS,
Ac GVHD III-IV 2.3%
cGVHD 6.8%
Mostly after failure of IS

Samarasinghe 2012
BJH
Background and Rationale of Upfront MUD HSCT

- Classical treatment algorithm of SAA forsees IST (ATG and CsA) if a MFD is not available.

- IST: very good survival rate but a fairly high rate of failures.

- Faulty hematopoiesis limits quality of life of children & adolescents.

- The option of HSCT from MUD as front-line treatment with no prior failed IST, never investigated so far in a comparative way in AA.
Upfront MUD HSCT study

• We therefore analysed the outcomes of a UK cohort of 29 consecutive children with idiopathic SAA who received unrelated donor HSCT as first-line therapy (i.e. they all lacked a MSD but then did not receive IST)

• Compared its outcome with historical matched controls who had received:
  (i) front-line MSD HSCT,
  (ii) front-line IST with horse ATG and ciclosporin
  (iii) MUD HSCT post IST failure as second-line therapy.
Characteristics of the UK Upfront HSCT cohort

29 consecutive SAA patients in 9 UK Centres
Upfront unrelated donor HSCT without prior IST,

Caucasian 86%
Males 41%.
Age at HSCT 8.46 yrs (1.73-19.11).
Source: 72 % BM, 28% PB

24 HLA-A,-B,-C,-DQ,-,DRB1 matched
5 1 Ag MM (2 HLA- A and 3 HLA-DQ)

Conditioning FCC (Fludarabine, Cyclophosphamide and Alemtuzumab)
plus low dose (3cGy) TBI for the MMUD HSCTs.

GVHD prophylaxis CsA +/-Mycophenolate
Follow Up 1.7 years (0.19-8.49)
Time to neutrophil Recovery

- Median time to neutrophil recovery following HSCT (>0.5 x 10⁹/l) was 18 days (range 9-29).
- Median time to platelet recovery (>50 x 10⁹/l) was 19 days (range 10-40).
- Median time from SAA diagnosis to neutrophil recovery (>0.5 x 10⁹/l) was 0.39 years (range 0.19-1.14).
Low Rates of GVHD with FCC HSCT SAA in upfront MUDs

• The 1 year cumulative incidence (CI) of grade II-IV acute GVHD was 10 ± 6%;

• There was only one case of grade III/IV acute GVHD (frequency of 3.5%) requiring systemic immunosuppressive therapy with steroids.

• The 1 year CI of chronic GVHD was 19 ± 8%

• Chronic GVHD was limited in all cases and restricted to skin and required topical therapy only.
Low Transfusion Requirements

• Viral reactivations were common (14/29 patients; frequency 48.3 %) but there were no cases of viral disease.

• Transfusion requirements were low; the median number of red cell transfusion units received were 5 (0-35) and the median number of platelet units received was 15 (1-95).

• The median hospital stay was 42 days (17-105 days).
Excellent Outcomes in Upfront Cohort

• There were two events, consisting of one primary graft failure following a HLA-A MMUD HSCT (with pre-existing anti donor HLA-A antibodies) who has now successfully received a second HSCT

• one death death due to idiopathic pneumonia syndrome post engraftment.

• The other 27 patients are in complete remission at last follow-up.

• The 2 year OS was 96% ± 4% and the 2 year EFS was 92% ± 5%.

• The median whole blood donor chimerism at last follow up was 100 % (range 88-100 %) and the median donor T-cell chimerism was 96.5 % (range 91-100 %).
Similar outcomes of Upfront Cohort with MFD HSCT

- 1 UD/3MFD HSCT. Matches: age, gender, source of stem cells, interval Dx- HSCT

Interval Dx- neutrophil recovery

UD 0.39 yrs vs. MFD 0.31 yrs p=0.93
Upfront Cohort superior to IST

1 UD HSCT/ 2 IST front-line

Matches: age, gender,

OS

UD 96%
IST 94%
p = 0.64

EFS

UD 92%
p = 0.0001
IST 40%
Upfront Cohort superior to MUD HSCT post IST Failure

1 MUD upfront/1 MUD post failed IST

Matches: gender,
  age at transplant,
  source of stem cells,

OS

MUD upfront 95%

MUD post IST 74%

p=0.02

EFS

MUD upfront 95%

MUD post IST 74%

p=0.02
Conclusions

• MUD HSCT is a good front-line option in children & adolescents with SAA.

• Caveats

  Start donor search at diagnosis

  Evaluate likelihood of MUD HSCT feasibility in ~2 months since diagnosis

  Careful discussion with family/pt of MUD vs IST

  Need for care in specialized AA haematology Centres
Time to Neutrophil recovery is similar following MUD and MSD HSCT

- The time from diagnosis to neutrophil recovery following IST was not available in our IST controls.

- At 3 months - 62 %
- At 6 months - 68% of adult patients respectively do show cellular recovery.

- Time to cellular recovery lower in children
- 3 months - 46%
- 6 months - 60%

- Time to cellular recovery similar to upfront MUD HSCT data.
Likelihood of finding a unrelated donor

- Caucasian patients have the highest likelihood of finding a matched unrelated donor (~75 % chance of finding a 8/8 matched unrelated donor. Eapen NEJM 2014)

- Blacks from South American or Central American backgrounds have the lowest likelihood of finding a well matched unrelated donor (~16 % chance), with other ethnic minorities having an intermediate likelihood.

- Thus, for many patients from ethnic minorities, upfront unrelated donor HSCT may not be an option.
Limitations of Upfront Data

• Our study is limited by its retrospective analysis with the potential for selection bias.

• Ideally, there would be a prospective randomised study comparing in children unrelated donor HSCT with MSD HSCT and IST as first-line therapy.

• Long Term follow up data required for upfront MUD data
## Pros and Cons of Early MUD HSCT

### Table 4 Considerations for early SCT in the SAA patients

<table>
<thead>
<tr>
<th>Benefits of early HSCT</th>
<th>Disadvantages of early HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earlier neutrophil recovery</td>
<td>Transplant-related mortality from advanced GVHD</td>
</tr>
<tr>
<td>Reduction in secondary clonal hematopoietic disorders</td>
<td>Treatment-related mortality from conditioning regimens</td>
</tr>
<tr>
<td>Curative with marked reduction in relapse compared with IST</td>
<td>Infectious complications from profound immunosuppression with transplant</td>
</tr>
<tr>
<td>Improved outcomes compared with transplantation after multiple failed treatments</td>
<td>Prolonged hospitalization required with transplantation</td>
</tr>
<tr>
<td>Reduction in graft failure rates</td>
<td></td>
</tr>
<tr>
<td>Reduction in transfusion burden?</td>
<td>Increased up front cost of transplant?</td>
</tr>
<tr>
<td>Reduction in economic burden?</td>
<td></td>
</tr>
<tr>
<td>QOL benefits?</td>
<td></td>
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Abbreviations: HSCT = hematopoietic SCT; QOL = quality of life; SAA = severe aplastic anemia.
Previous Barriers to Upfront MUD HSCT have reduced

• The previous barriers to upfront MUD HSCT are now considerably reduced.
  1. severe GVHD
  2. graft failure
  3. treatment related mortality
UK Algorithm for Idiopathic Paediatric SAA

- Establish diagnosis of SAA/νSAA
- Exclude inherited bone marrow failure syndrome
- Tissue type family and patient

[Diagram]

1st Choice
- MSD HSCT
- If no HLA Identical Sibling available, perform unrelated donor search

2nd Choice
- IST with Horse ATG (if available)/ciclosporin or 10/10 MUD HSCT (if donor available)
  - Assess response to IST at 3–4 months. If fails Horse ATG, should have MUD HSCT. If lacks a MUD then proceed to 3rd choice

3rd Choice
- IST with rabbit ATG/ciclosporin or mismatched unrelated donor HSCT (9/10)
  - If fails rabbit ATG, or suitable MMUD not available, then proceed to 4th choice

4th Choice
1. Alemtuzumab or Cyclophosphamide
2. Haploidentical or unrelated donor umbilical HSCTs
3. Repeat course of IST
<table>
<thead>
<tr>
<th>Absolute</th>
<th>Patient Factors</th>
<th>Strongly Recommended</th>
<th>Patient Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening Infections</td>
<td>Donor availability within 5 months of diagnosis. Preferably within 3 months</td>
<td>Presence of cytogenetic strongly suggestive of MDS e.g. monosomy 7 (alternative conditioning regimen suggested)</td>
<td>Recurrent Infections/Temperatures</td>
</tr>
<tr>
<td>Age of donor &lt;45 years but preferably &lt; 30 years</td>
<td>Ideally Bone marrow as stem cell source</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avoid multiparous female donors</td>
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</tbody>
</table>
In Vivo T cell Depletion superior with Alemtuzumab

Multivariate analysis for OS. Considering ATG as the standard, OS was worse with no serotherapy \( (p=0.001) \) and better with Alemtuzumab \( (p=0.037) \); Alemtuzumab vs no serotherapy

Samarasinghe et al. Blood 2015;126(23): 1210
Treatment Recommendation for MUD HSCT

- Matched Unrelated donor HSCT (10/10 HLA-A, -B, -C, -DRB1,-DQ)
- Indications:
  - In the absence of MSD and either upfront (i.e. without prior ATGAM) or following ATGAM failure at 3-4 months
- Conditioning Regimen
  - Fludarabine 30 mg/m²/day for 5 days: day -7 to day -3
  - Cyclophosphamide 60 mg/kg/day for 2 days: days -3 to -2
  - Alemtuzumab 0.3 mg/kg/day for 3 days: days –6 to -4
  - GVHD prophylaxis- Ciclosporin only as above
  - Stem Cell Source- First line- Bone Marrow
  - Second Line- Peripheral Blood Stem cells
- Screen for anti HLA antibodies in the recipient to the donor
Clinical Scenario

- 10 year old boy with idiopathic SAA.
- Caucasian. No MSD
- 2 potential MUD (German Male 24 and UK male 32)
- Do you go for ATGAM now or go for the MUD transplants
Clinical Scenario 2

- 12 year old boy with idiopathic SAA

- 2 donors. 1 MUD US Female 49 multiparous and one US male 54

- Numerous MMUDs

- ATGAM or MUD
Future Algorithm for Paediatric SAA

1. Establish Diagnosis of SAA
2. NGS Panel/SNP Array for MDS mutations/Telomere lengths
   - IBFM
   - Acquired SAA

   1. Low Risk for Clonal Evolution
   2. High Risk for Clonal Evolution

3. 1st Line - Matched Sibling HSCT
4. 2nd Line
   - IST with Horse ATG
   - MUD HSCT