Hematopoietic Stem Cell Transplantation for patients with Severe Aplastic Anemia

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Acquired Aplastic Anemia

- Empty or hypoplastic marrow
- Peripheral blood cytopenia
- ANC < 0.5 x 10^9/L
- Platelets < 20 x 10^9/L
- Reticulocytes < 20 x 10^9/L
- Immune mediated suppression of hematopoiesis
Aplastic Anemia – Differential Diagnosis

- Fanconi Anemia
- Dyskeratosis Congenita
- PNH
- Hypoplastic MDS
- ALL

- DEB/Mitomycin test – Fanconi
- Telomere Length – DC
- Bone Marrow Cytogenetics – Hypoplastic MDS
- Flow Cytometry for PNH
Treatment of Acquired Aplastic Anemia

- Severity of pancytopenia
- Patient’s age

- HSCT from a matched sibling is the treatment of choice for patients < 40ys with SAA
  - If there is no matched sibling donor: IST is recommended
  - If you fail 1st IST: URD BMT / 2nd IST is recommended
Supportive treatment

- Leucodepleted blood products. Irradiated during IST
- CMV negative blood products until you know CMV status
- G-CSF: Only for short periods during severe infections.
- Anti-fungal prophylaxis: neutrophil count is < 500/ul.
- Prophylactic antibiotics are not routinely recommended (cipro/levo)
- Febrile neutropenia: immediate: empirical broad-spectrum antibiotics
- Granulocyte infusions: Severe refractory sepsis or fungal infection
- Iron chelation if necessary

S.Samarasinghe and D Webb BJH 2012
Hla Matched Sibling
Outcome of pts with acquired aplastic anemia given 1st line BMT or IST treatment in the last decade: EBMT report

Locasciulli et al Hematologica 2007; 92:11
EBMT Data on 1886 pts transplanted from MSD 1999 – 2009 
Bacigalupo et al Hematologica 2012

Graph showing survival rates:
- <114 days from diagnosis; n=941: 84%
- ≥114 days from diagnosis; n=945: 72%
- Age < 20, n=996: 87%
- Age ≥ 20, n=890: 70%

P < 0.0001
Preparatory regimen: To ATG or not ATG; that is the question...

148 children – Seattle 1971-2010

**Bacigalupo Hematologica 2012**

**Burroughs et al BJH 2012**
Data from Curitiba (500 pts transplanted since 1979) BMT for pts < 19 yrs old with SAA – age > ou ≤ 10

CFA 200mg/kg

Overall Survival: 87%
33/38 pts: 1 – 15 years (M: 10 yrs)

Overall Survival: 70%
52/75 pts: 1,1-15 yrs (M: 7 yrs)

p = 0.24

CY 200mg/kg:
< 15 previous transfusions

BU12mg/kg + CY120mg/kg:
> 15 previous transfusions

p = ns
Prep regimen and GVHD prophylaxis  HLA Matched Siblings

- CY 200mg/kg +/- ATG is the recommended prep regimen
- CSA alone is related to worse prognosis and CSA+MTX is the recommended GVHD prophylaxis
- Recent data on Alemtuzimab (Campath) - MTX may be omitted
- Is there a superiority of hATG over rATG?
  - Single center study
  - CIBMTR data – Tandem Meetings 2014
Chimerism and Weaning Immune Suppression

- Mixed chimerism is frequent (CY+/- ATG protocol)
- It may predict graft loss, although most pts with mixed chimerism will retain their grafts
- Instable chimerism – predicts graft loss
- Usually occurs during weaning of immunosuppression
- Wean late and wean slowly
- Late graft failures can usually be rescued with a 2nd transplant

Stella Davies 2009
Immunosuppressive Treatment
So, if you don’t have a MSD....

- Predictors of response
  - Very severe aplastic anemia (Fuhrer et al, 2005)
  - Younger age
  - Higher pre-treatment reticulocyte count and lymphocyte count (Scheinberg et al, 2008)
  - Male gender; leucocyte count (Yoshida et al, 2011).
  - Time interval from diagnosis to treatment (Yoshida et al, 2011)
  - Telomere length (Scheinberg, 2010)

S.Samarasinghe  BJH 2012  
Scheinberg et al. Einstein 2011(9):229-35
Indications for IST – Worldwide experience

Indications\(^1\):

- Pts with SAA > 40 ys
- Pts < 40ys without and HLA matched sibling
- Pts with non severe AA

Treatment::

- Csa + hATG
- Csa + rATG

- Curitiba : Csa + Prednisone (without ATG)
  - Dr Larissa Medeiros/ Dr Ricardo Pasquini

Horse x Rabbit ATG: Better results for the Horse ATG group

- IST with horse ATG is superior to rabbit ATG.
- IST with horse ATG leads to a better overall response rate
- Risk of relapse (10% at 10 years)
- Risk of development of clonal abnormalities (10-15%), without a plateau
- Relapse after successful IST has a 60–70% response to a 2\textsuperscript{nd} course of IST.

Marsh et al Blood 2012

S.Samarasinghe BJH 2012
IMMUNOSUPPRESSIVE THERAPY WITH CYCLOSPORINE AND PREDNISONE FOR PTS WITH ACQUIRED APLASTIC ANEMIA: 20 YEAR FOLLOW UP AND ANALYSIS OF FACTORS PREDICTING RESPONSE
SINGLE CENTER STUDY: CURITIBA – PR BRAZIL

Apresentação e Defesa de Dissertação para obtenção do grau de Mestre no Curso de Pós-Graduação em Medicina Interna do Departamento de Clínica Médica, Setor de Ciências da Saúde, Universidade Federal do Paraná.

Orientador: Prof. Dr. Ricardo Pasquini
## Patient Characteristics : 384 pts

<table>
<thead>
<tr>
<th>Características</th>
<th>Resultados</th>
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<tbody>
<tr>
<td>Period</td>
<td>dec/1988 - dec/2008</td>
</tr>
<tr>
<td>Age ( Median)</td>
<td>21 ys (2-75)</td>
</tr>
<tr>
<td>Gender</td>
<td>215 M:169 F</td>
</tr>
<tr>
<td>White Race</td>
<td>80% (307)</td>
</tr>
<tr>
<td>Disease duration ( Median)</td>
<td>95 dias (2-4749)</td>
</tr>
<tr>
<td>Transfusions (Median)</td>
<td>12 (0-200)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>- Idiopathic</td>
<td>300</td>
</tr>
<tr>
<td>- Other</td>
<td>84</td>
</tr>
<tr>
<td>Follow up ( Median)</td>
<td>7 ys (0.02 - 23)</td>
</tr>
<tr>
<td>Severity of Disease</td>
<td>Number (n)</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Non Severe</td>
<td>79</td>
</tr>
<tr>
<td>Severe</td>
<td>217</td>
</tr>
<tr>
<td>Very Severe</td>
<td>80</td>
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*p < 0.001*
OS x response to treatment at 2 ys

RC (n=143) 94%±2
RP (n=53) 78%±7
SR (n=36) 37%±9

P<0,001

Courtesy Dr Larissa Medeiros
Overall Survival
Children, Adolescents and Adults

10-18ys (n=93) 62%±6
<10ys (n=55) 61%±7
>18ys (n=236) 61%±4

p=0.842

Courtesy Dr Larissa Medeiros
Cumulative Incidence of clonal evolution
( Median follow up: 10ys (2-19) )

12%±3 (n=29)

Courtesy Dr Larissa Medeiros
What about the algorithm?

S.Samarasinghe et al BJH 2012
Unrelated HSCT
Unrelated HSCT for SAA

- Is a very effective treatment but it is limited by:
  - Availability of a suitably matched unrelated donor
    - HLA matters: 118 children transplanted between 1989-2003; TRM was higher in mismatched donors
    - OS after 8/8 MUD was better
  - Higher risks of graft failure, and graft-versus-host disease,
  - Higher mortality

Mary Eapen BBMT 2011
Excellent outcome of MUD transplantation in pediatric aplastic anemia following failure with IST: a UK multicentre retrospective experience

S.Samarasinghe et al BJH 2012
Excellent outcome of MUD transplantation in pediatric aplastic anemia following failure with IST: a UK multicentre retrospective experience

S.Samarasinghe et al BJH 2012
Prep Regimens

- EBMT: FLU + CY1200 mg/m2 + rATG 7,5mg/kg +/− 2Gy TBI
  - High incidence of PGF and PTLD
    - Bacigalupo et al 2005; 2010
- FLU + CY (120mg/kg), rATG 7,5 mg/kg + Rituximab and 2Gy TBI (＞15ys or sensitized).
  - Kojima et al, 2011
- Seattle: FLU + 2 Gy TBI+ hATG.
  - Deeg, 2002
- UK: CY(120) + FLU+ Campath
  - Samarasinghe et al, 2012
Prep Regimen in Brazil

- Initially: MAC regimens (CY + TBI +/- ATG)
  - Good engraftment but high toxicity. OS: 72%

- Bacigalupo Regimen:
  - CY 1200mg/m² + FLU+ATG: High incidence GF
    - Added TBI even for children
    - Increased the dose of CY to 60mg/kg
  - BU12mg/kg + CY 120mg/kg + rATG
    - Very good sustained engraftment
    - LTFU
Brazilian Experience: Curitiba, Jaú, Ribeirão Preto, Porto Alegre, Recife, São Paulo (GRAACC): 47 pts
(SBTMO data: 100 pts)

33/47 pts – OS: 70%
Follow up: 150 – 4300 days (M: 960 d)

Age: 2-19ys (M:11)
Overall Survival according to Myeloablative and Reduced Intensity Regimens

**MAC:** 18 pts – OS 72% at 5ys

**RIC:** 29pts – OS 69% at 3ys
Overall Survival according to HLA compatibility

*HLA comp: 39 pts – OS :74% at 3ys*

*HLA mismatch: 8 pts - OS :50% at 3ys*

*p: 0.07*
Cumulative Incidence of Graft rejection according to the type of Prep Regimen: 46 pts

**RIC:** CI of rejection 21%

**MAC:** No rejection   \( p: 0.03 \)
Unrelated Cord Blood Transplantation for pts with SAA: Curitiba

- 7 pts. Age: 1 and 17ys (M: 8ys)
- HLA compatibility: 5 pts (4/6 CB) and 2 pts (5/6 CB)
- 1 pt (17ys old) received a double cord after a non myeloablative regimen
- All the others received Myeloablative regimens (CY+TBI or BU+CY+ATG)
- All pts died between 4 – 529 days (M: 45 days). Only 1 pt engrafted. Death was related to infections in the majority of patients.

- Brazilian Data: total of 16 pts. Median age: 8 (only 2 >17)
  - Only 2 pts are alive (RIC and MAC). Majority of deaths occurred < 1y and were related to rejection and infections. 5 pts engrafted (4 MAC)
  - 11/16 received MAC regimen.
Stem cell source: No matter how you analyze PBSC is always related to worse outcome *Bacigalupo et al 2012*

<table>
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<th>1886 pts</th>
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<tr>
<td>Bone marrow (n=1163)</td>
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<tr>
<td>Peripheral blood (n=723)</td>
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Stem Cell Source

- Cord Blood Transplantation
  - High graft failure and TRM
  - OS in the two largest retrospective analyses to date have ranged from 30% to 40% (Yoshimi et al, 2008; Peffault de Latour et al, 2011).
  - Improved results were seen with higher total nucleated cell
    - OS was 45% for TNC > 3.9x 10^7/kg vs. 18% for TNC < 3.9x 10^7/kg; (Peffault de Latour et al, 2011).
Final Comments

- Discuss the algorithm for treatment of Aplastic Anemia in Children and adolescents
- Consider MUD (10/10 HR) transplant earlier (3-6m after beginning IST)
- Discuss prep regimens:
  - RIC regimen: CY (dose?) + FLU + ATG + /-TBI200
  - Other regimens: BU12+CY120+ATG
- Second questions: IST after transplant (type and duration), chimerism analysis, co-infusion of MSC and so on
Thank you !!!

- HC UFPR BMT team – Bone Marrow Failure Clinic (Adult and Pediatric team)
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- All Brazilian BMT Centers that sent us information about their pts
## Resultados – Sobrevida Global

<table>
<thead>
<tr>
<th>Número de Transfusões</th>
<th>Porcentagem de Reticulócitos</th>
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<tbody>
<tr>
<td>&lt; 15 (n=211) 69±4</td>
<td>≥ 0,5 % (n=195) 76±4</td>
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<tr>
<td>≥ 15 (n=163) 55±4</td>
<td>&lt; 0,5 % (n=177) 50±4</td>
</tr>
</tbody>
</table>

p=0,027

p<0,001
**Resultados – Sobrevida Global**

Número de Neutrófilos

- >500 (n=203) 71%±4
- 200-500 (n=93) 59%±6
- <200 (n=78) 44%±6

p<0,001

Número de Plaquetas

- ≥ 12.000 (n=197) 69%±4
- <12.000 (n=179) 55%±4

p=0,002