Hematopoietic Stem Cell Transplantation for patients with Severe Aplastic Anemia

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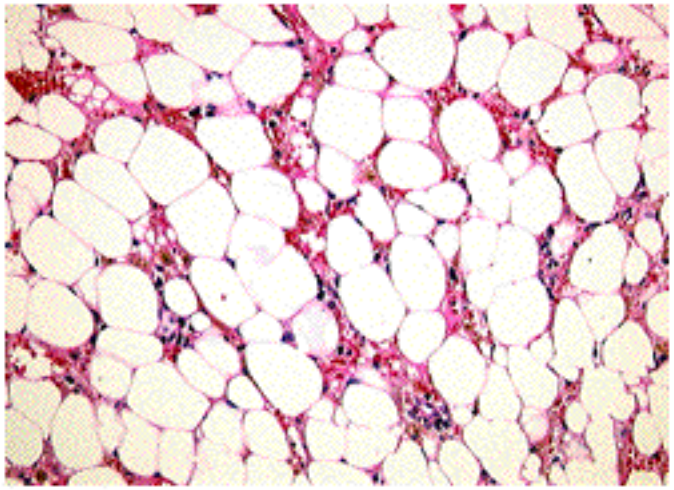
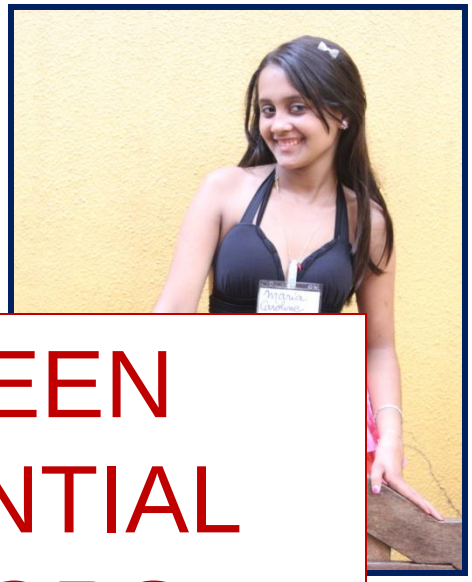
Acquired Aplastic Anemia

- 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

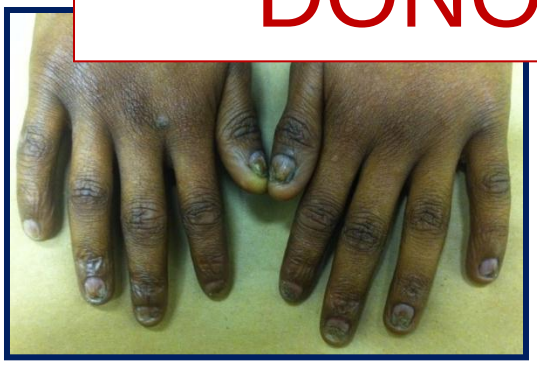


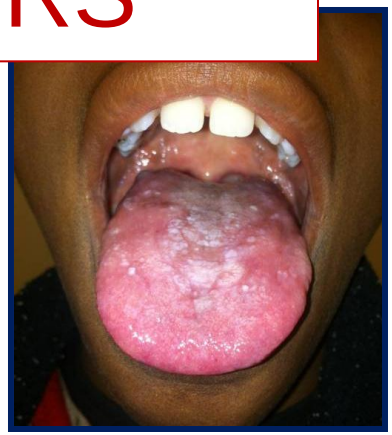
Aplastic Anemia – Differential Diagnosis

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



SCREEN POTENTIAL DONORS





- 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

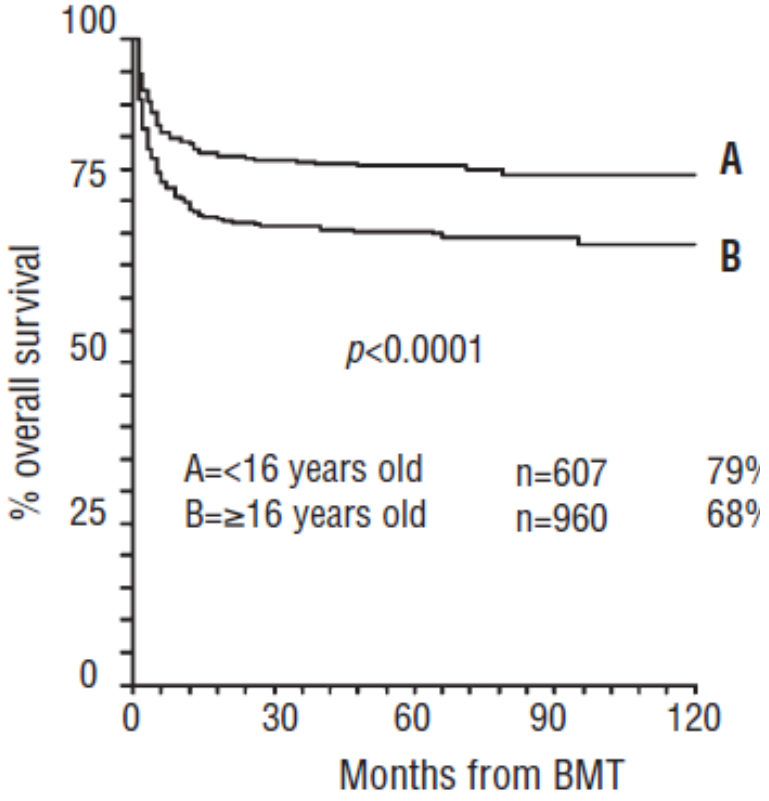
Supportive treatment

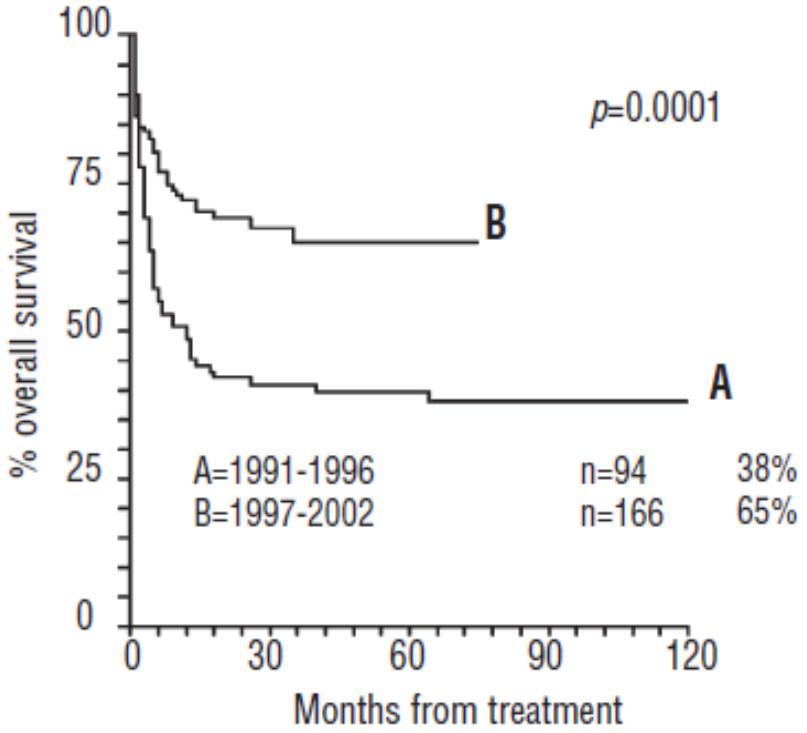
- Leucodepleted blood products . Irradiated during IST
- CMV negative blood products until you know CMV status
- G-CSF: Only for short periods during severe infections.
- Anti-fungal prophylaxis : neutrophil count is < 500/ul.
- Prophylactic antibiotics are not routinely recommended (cipro/levo)
- Febrile 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

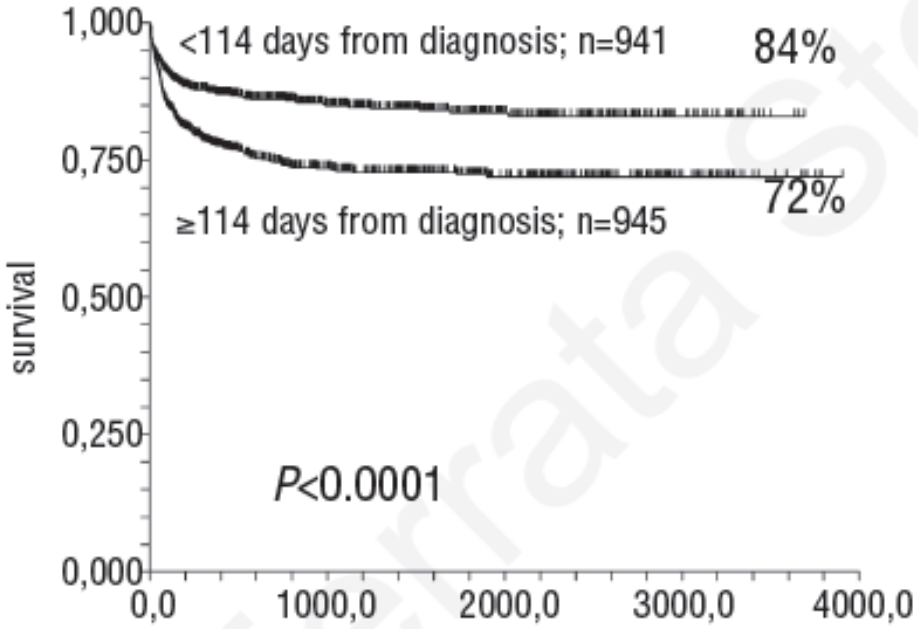
Outcome of pts with acquired aplastic anemia given 1st line BMT or IST treatment in the last decade: EBMT report

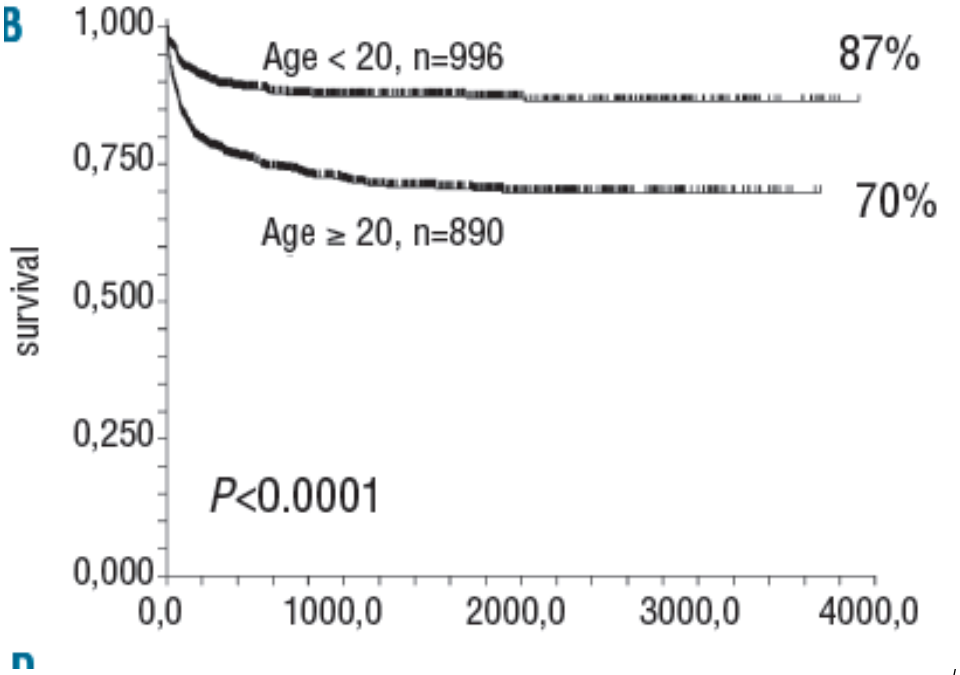




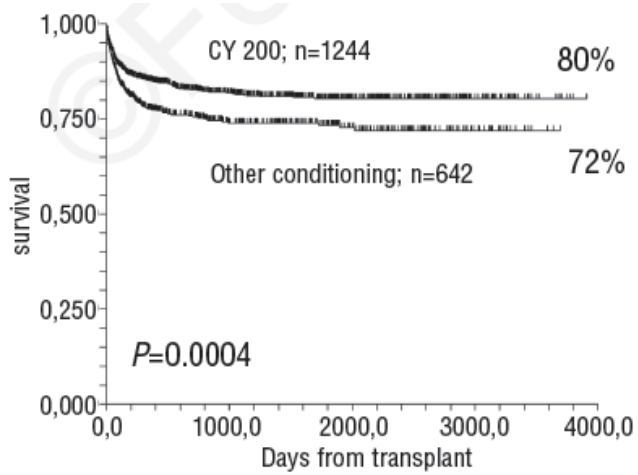
Locasciulli et al Hematologica 2007; 92:11

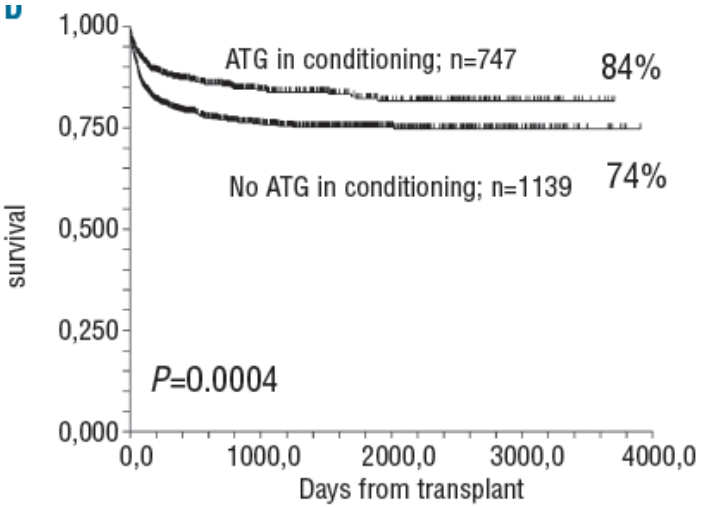
EBMT Data on 1886 pts transplanted from MSD 1999 – 2009 *Bacigalupo et al Hematologica 2012*





Preparatory regimen : To ATG or not ATG; that is the question…





148 children – Seattle1971- 2010

Bacigalupo Hematologica 2012

Burroughs et al BJH 2012

Data from Curitiba (500 pts transplanted since 1979) BMT for pts < 19 ys old with SAA – age > ou ≤ 10

CFA 200mg/kg

Overall Survival: 87%

33/38pts :1 – 15 years(M: 10ys)

$p=0,24$

Overall Survival:70%

52/75pts - 1,1-15 ys(M:7 ys)

$p=ns$

CY 200mg/kg:

< 15 previous transfusions

BU12mg/kg+CY120mg/kg:

> 15 previous transfusions

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 immunosupression
- Wean late and wean slowly
- Late graft failures can usually be rescued with a 2nd transplant

Stella Davies 2009

Immunosupressive 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*

1.Marsh J et al, British Journal of Haematology 2009;147:43

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 2nd course of IST.

Marsh et al Blood 2012

S.Samarasinghe BJH 2012

LARISSA ALESSANDRA MEDEIROS

IMMUNOSUPRESSIVE 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

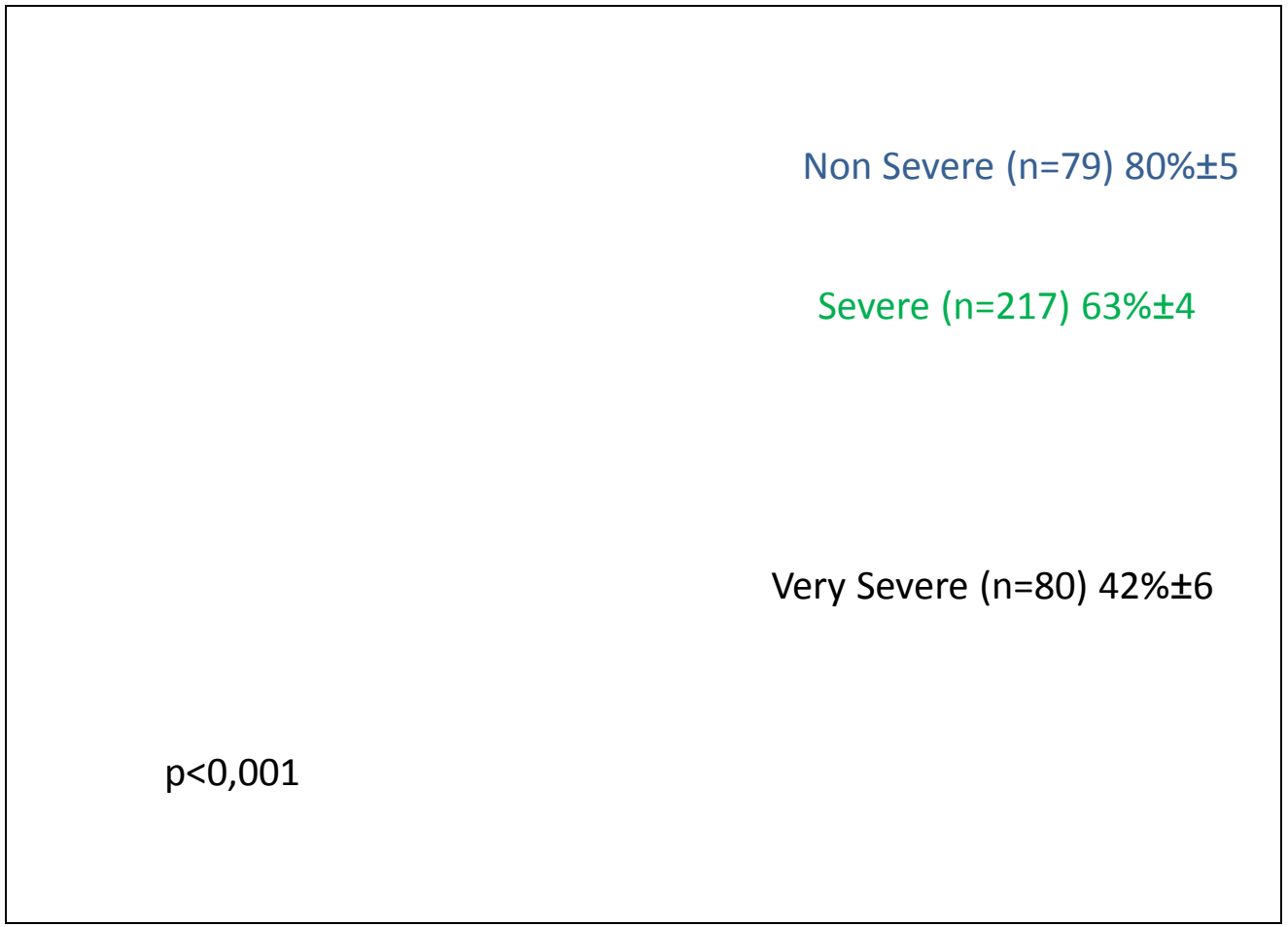
Apresentação e Defesa de Dissertação para obtenção do grau de Mestre no Curso de Pós-Graduação em Medicina Interna do Departamento de Clínica Médica, Setor de Ciências da Saúde, Universidade Federal do Paraná.

Orientador: Prof. Dr. Ricardo Pasquini

Patient Characteristics : 384 pts

Características	Resultados
Period	dec/1988 - dec/2008
Age (Median)	21 ys (2-75)
Gender	215 M:169 F
White Race	80% (307)
Disease duration (Median)	95 dias (2-4749)
Transfusions (Median)	12 (0-200)
Etiology	
- Idiopathic	300
- Other	84
Follow up (Median)	7 ys (0,02 - 23)

Results: Overall Survival x Severity of disease



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

Marsh et al BHJ 2009

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

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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*

Bacigalupo 2010

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, Sao Paulo (GRAACC) : 47pts
(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*

1886 pts
Bone marrow (n=1163)
Peripheral blood (n=723)

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)
- Imunogenética: N.F. Pereira, L. Pangracio, M Kleina
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- Hospital Real Português – Dr Rodolfo Calixto
- Hospital de Clínicas da UFRS – Dra Liane Daudt e Dr Lauro Gregianin
- INCA – Dr Luis Fernado Bouzas e Leonardo Arcuri (SBTMO – Unrelated HSCT data)
- All Brazilian BMT Centers that sent us information about their pts

Resultados – Sobrevida Global

Número de Transfusões

<15 (n=211) 69%±4

≥ 15 (n=163) 55%±4

p=0,027

Porcentagem de Reticulócitos

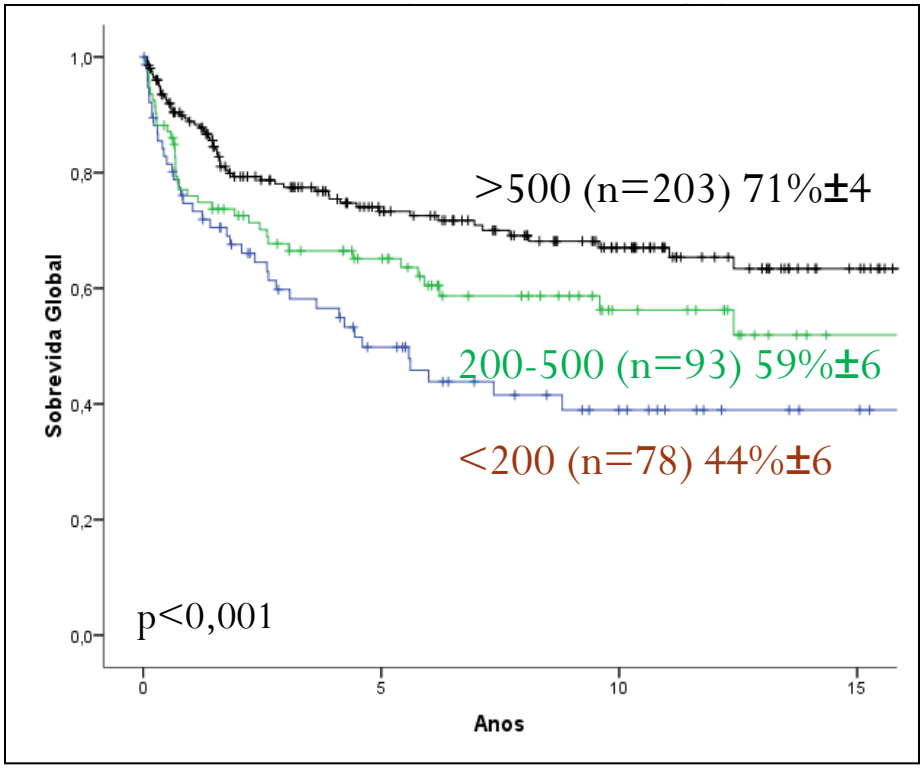
≥ 0,5 %(n=195) 76%±4

< 0,5 %(n=177) 50%±4

p<0,001

Resultados – Sobrevida Global

Número de Neutrófilos



Número de Plaquetas