How do I treat Acquired Aplastic Anemia in Children

Carlo Dufour

2nd Educational on SAA. Budapest 1-3 November 2012

The European Group for Blood and Marrow Transplantation

- EPIDEMIOLOGY & DIFFERENCES WITH ADULTS
- SPECIFIC TREATMENT
- EBMT STUDY
- SUPPOPORTIVE TREATMENTS
- NON SEVERE AA
- ALGORITHM
EPIDEMIOLOGY of AA in CHILDREN

- AA in childhood is rarer than in older ages
- Estimated Occurrence in Western Countries
- Three times higher in Far East
EPIEMIOLOGY of AA in CHILDREN

- AA in childhood is rarer than in older ages
- Estimated incidence in Western Countries 2-3/million/year
- Three times higher in East Asia

DIFFERENCES WITH AA of ADULTS

- Higher rate of undetected genetic MF diseases
  5-10% are hidden/misdiagnosed inherited Marrow failure diseases:
  TERC, TINF2, TERT, cMPL

- High proportion of RC (56-81%) with hypocellular marrow

- VSAA better outcome than SAA
  (Fuhrer et al, Blood 2005)
- EPIDEMIOLOGY & DIFFERENCES WITH ADULTS
- SPECIFIC TREATMENT
- EBMT STUDY
- SUPPOPORTIVE TREATMENTS
- NON SEVERE AA
- ALGORITHM

SPECIFIC TREATMENT

- HSCT from MDS
- IST
- HSCT from MUD
- ALTERNATIVE DONOR HSCT
- SALVAGE NON HSCT OPTIONS
**HSCT from MSD**

First choice treatment if donor available

85%- 100% OS  
Kojima 2000, Borroughs 2012

Conditioning
Cy 200 mg/kg
ATG
Mtx + CsA

**PROBLEMS**

• cGVHD most important negative factor for LT surv  
Sanders 2011

Evidence that Alentuzumab reduces cGVHD.  
Marsh 2011

Ongoing study of SAAWP EBMT

• Late rejection  
Monitor chimerism and CsA for 12 months after HSCT

• Late effects  
Malignancies in 7-13% cases  
(Kahl 2005, Sanders 2011)  
GVHD &TBI major risk factors  
Avascular necrosis and encocryne dysfunction  
R P de La Tour Hematologica 20012

**IST**

First choice treatment if MUD not available within 3-4 months

ATG (Horse) + CSA  
~80% OS,  
60-70% Response,  
10-33% Relapse  
S Samarasinghe 2012

No benefit by adding MMF or sirolimus

Good prognostic factor  
Younger, high rets & lympho count, < 2x10^9/l WBC tot, VSAA

CSA for 1 yr and than slow tapering to lower relapse  
Saracco 2009
CSA: slow taper off

- Slow Tapering (<0.3–0.7 mg/kg/month) lower risk of relapse vs
- Rapid Tapering ≥0.8 mg/Kg/month

P. Saracco, Marrow failure group AIEOP, Br J Haematol 2008

IST

PROBLEMS

- **Clonal evolution** (8.5-15% AML at 10 yrs no plateau. No long-term G-CSF

- **Treatment Failure** (no response/relapse) 13-33% (Samarasinghe, 2012)

  Re-treatment with ATG possible but worse than MUD Kioaka Blood 2008
**HSCT from MUD**

### Strong improvement in the last 2 decades

- OS 57% - 83%
  - Perez Albuerne 2008
  - Kennedy-Nasser 2006
- Pediatric studies

- Perez Albuerne 2008
- Kennedy-Nasser 2006

Kosaka Y et al., Blood 2008, Feb 1; 111(3): 1054-9

Failure Free Survival (survival with response at 5 years) is far better after HSCT from Alternative donors than after second IST.

---

**HSCT from MUD**

### Conditioning “EBMT like”

- <15 yr not sensitized
  - Flu 120mg/kg + Cy 120 mg/Kg + ATG + Rituximab (LPD proph)
- ≥15 yrs, sensitized
  - As above plus TBI 2Gy
  - Mtx + CsA

- No irradiation
  - Flu 120mg/kg + Cy 120mg/kg + Alentuzumab 0.9 mg/kg

- 95% 5 yr FFS,
- Ac GVHD III-IV 2.3%
- cGVHD 6.8%

- Mostly after failure of IS

Samarasinghe, 2012
**CELL SOURCE IN MUD**

![Graph showing cell source in mud for different age groups.](image)

The risk of extensive chronic GvHD is 3% for BM and 20% for peripheral blood (PB)

BM better than PB. Use BM

*Bacigalupo A et al. Haematologica 2012*

**SALVAGE- NON HSCT- OPTIONS**

**Alemtuzumab**

- Transient response in 50% of patients.
- Viral infection load acceptable

*Ristiano AM et al. SAAEBMT Br J Haematol. 2010*

**Cyclophosphamide** 50 mg/kg/day i.v. for 5d without HSC rescue.

- 62% OS
- 48% EFS,
- Patients non responsive or refractory to 2 or 3 courses of IST
- 50% risk of infection, often lethal.

*Brodsky et al. Blood 2010*

**Eltrombopag**

- Response 41%.
- Normalization of tri-lineage hematopoiesis and cellularity in some cases
- Limited side effects, no fibrosis
- ORAL!
- Expands the hematopoietic stem cell compartment

*Dunbar C. NEJM 2012*
SUPPORTIVE TREATMENTS

- Transfusions
- Chelation
- G-CSF
- Antibiotics
- Antifungal

TRANSFUSIONS

- **Restrictive policy**

- **Platelet concentrates:**
  - therapeutic transfusion in case of significant bleeding
  - prophylactic transfusion when the platelet count is $< 10 \times 10^9/L ( < 5 \times 10^9/L)$ or
    $< 20 \times 10^9/L$ in the presence of fever, infections or
    $< 50 \times 10^9/L$ during ATG treatment

- **Red blood cell concentrates:**
  - hypoxic anemia
  - based on symptoms and co-morbidities; quality of life
TRANSFUSIONS

- Leukoreduced blood products to prevent HLA alloimmunisation
- Irradiated products to prevent transfusion associated GVHD (higher risk with ATG) and to reduce sensitization to HLA and non-HLA Antigens from multiple transfusions. Until lympho ≥1.0 x 10^9/L.
- Granulocyte transfusions in case of severe infections to bridge the gap until neutrophil recovery.

IRON CHELATION

- Desferoxamine and deferasirox. Avoid deferiprone for agranulocytosis. Erythroid recovery may benefit
- Careful monitor of renal function if deferasirox used with CsA. Avoid undue reduction of CsA
- Anti fungal prophilaxis (fluconazole and posaconazole) reduced fungal related mortality.
INFECTION PREVENTION

• No studies in children with AA.

• Data derived from adult neutropenic patients after chemo. But not from AA patients!

• 46% FUO

54% documented infections

Microbiologically documented 50%
Clinically Documented 42%

sepsis, skin/soft tissue, pneumonia.

Invasive Fungal 8%

• Risk of documented infections 21% equal prior and after d 120
50% of episodes within the first 24 days.

• Significant association with the severity

• No association with response at day 120 and 180 and G-CSF

• Mortality attributable to infections 9%,

23

24
INFECTION PREVENTION

G-CSF

- No difference in OS, EFS, Response, Mortality, Clonal disease
- Identifies responders: pts achieving PNM > 0.5 x10^9/l within first 30 days have better survival and higher chances of response

![Graph showing survival probability over time](image)

- Reduction of infections and hospitalization days
  Tichelli A et al SAAWP EBMT, Blood 2011

- No favourable association with low occurrence of infections in children
  Quarello P Eur J Haematology, 2012

INFECTION PREVENTION

- According to Center policy
- In general no long term antibiotic prophylaxis
- TMP-SMZ or Pentamidine for PCP prophylaxis
- Some recommend Anti fungal prophylaxis (fluconazole, itraconazole or posaconazole) when Neutrophils < 0.5x10^9/l
  Robenshtok et al., J Clin Oncol. 25:5471 5489 (2007)
- G-CSF in case of infections in neutropenic phase

26
• EPODEMOIOLOGY & DIFFERENCES WITH ADULTS
• SPECIFIC TREATMENT
• EBMT STUDY
• SUPPORPTIVE TREATMENTS
• NON SEVERE AA
• ALGORITHM

NON SAA

• Spontaneous resolution 12% (Howard, Ped Blood & cancer2004)
• Tend to progress to SAA
  67% if only on supportive treatment (Howard, Ped Blood & cancer2004)
  5.3% on Danazole (Wang, SC China study 2011)
• If transfusion Independent and PNM > 0.5 x10^9/l observation
• If transfusion dependent OR PNM < 0.5 x10^9/l treat as SAA
ALGORITHM

DIAGNOSIS

HLA id SIB

NO

Start unrelated donor search and if MUD unlikely TREAT with IS

ATGAM 40mg/Kg/d x 4d
CSA 5mg/Kg/d
G-CSF mcg/Kg/d first 30 d

Evaluate at month + 4
NO RESPONSE/ RELAPSE

HSCT

Cy 200x5
ATG, CSA, MTX

YES

HLA id UNREL DONOR

NO

Rabbit ATG, CSA, vs 9/10 MM UD

HSCT

NO RESP. RELAPSE

>1 Ag MM FAMILY/HAPLO HSCT/CB
or Experimental IS (Campath, CY with no rescue, Etanercept)