Disease Updates: Aplastic Anemia

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• Definition

• What is new in:
  • Diagnosis
  • First line treatment
    HSCT
    IST
  • Second line treatment
    HSCT
    IST
  • Supportive treatment
  • Salvage
AA-DEFINITION

Haematopoietic cellularity (trephine biopsy) < 30%  
+ at least two of the following:

• Reticulocytes < 1% or < 60,000, and/or

• Platelets < 20,000 and/or

• ANC 1000-500 (moderate), < 500 (severe), < 200 (very severe)

and

• < 5% blasts
• No major dysplastic signs
• Possible chr abnormalities (10% ca)

• Rare disease
• 1 case /million inhabitants /year
• Introduction

• What is new

• Diagnosis
  • First line treatment
  • Second line treatments

• Experimental treatments
Differential Diagnosis

Importance of identifying diseases that may mimick AA

**Hypocellular MDS/Acute Leukemia**

<table>
<thead>
<tr>
<th>Aplastic Anemia</th>
<th>Hypocellular MDS/Leukemia</th>
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<tbody>
<tr>
<td><strong>Dysplasia</strong></td>
<td>No major</td>
</tr>
<tr>
<td><strong>Blasts</strong></td>
<td>Absent</td>
</tr>
<tr>
<td><strong>CD 117+</strong></td>
<td>Absent</td>
</tr>
<tr>
<td><strong>CD 34+</strong></td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Marrow</strong></td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td></td>
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<tr>
<td><strong>Cytogenetic Clone</strong></td>
<td>Rare (~10%)</td>
</tr>
<tr>
<td><strong>PNH clone</strong></td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Spenomegaly</strong></td>
<td>Absent</td>
</tr>
</tbody>
</table>
Immunohistochemistry for CD 34+ cells. No evidence of blasts
Blasts in clusters in HYPOCELLULAR AML

THIS IS NOT APLASTIC ANEMIA

CD 34+ cells in HYPOCELLULAR AML
MORE SOPHISTICATED TOOLS

• SNP-A identifies cryptic clonal genomic aberrations in AA and hMDS that may help to identify the two diseases. Afable MG II et al, Blood 2011.

• Distinct cytokine profile in PB may differentiate AA from hMDS (> thrombopoietin and chemokine (C-C motif) ligand 3). Feng X, Haematologica 2011.

In the future may be helpful to better discriminate the two diseases

Currently not in the standard practice.
Importance of identifying diseases that may mimic AA

Congenital marrow failure syndromes

Fanconi Anemia (FA)
Dyskeratosis Congenita (DC)
Congenital Amegakaryocytic Thrombocytopenia (CAMT) in aplastic phase
Diamond Blackfan anemia (DBA),
Shwachman Diamond syndrome (SDS),
Il 25% dei pazienti ha un fenotipo somatico normale o quasi.

Non classical FA phenotype of FA pts

Courtesy from Eliane Gluckman
Differential Diagnosis

Importance of identifying diseases that may mimic AA

Congenital marrow failure syndromes

Fanconi Anemia (FA)
Dyskeratosis Congenita (DC)
Congenital Amegakaryocytic Thrombocytopenia (CAMT) in aplastic phase
Diamond Blackfan anemia (DBA),
Shwachman Diamond syndrome (SDS),
PATIENT 1

14 yr old boy

WBC 2.7 x10^9/l, ANC x1.0^9/l, Hb 14 g/dl, Plts 73 x10^9/l

Hypocellular marrow

Non SAA

Never requiring transfusions

Normal somatic phenotype

TERC mutation c 53 T>A that changes the telomeric sequence

wt: TTAGGG

TERC c53T>A

TTTGGG

AA due to TERC mutation (DC)
• I:1 Died for Acute Leukemia at age of 46, TERC mutation carrier?

• I:2 Healthy, no TERC mutation

• II:1 TERC pt 1, Aplastic anemia with TERC mutation (TERC c53T>A) onset at age 14 (now is 23).

• II:2 17 year old boy, TERC mutation carrier, (TERC c53T>A)
Phenotypically and haematologically normal, so far
HLA Identical to TERC Pt 1

Diverse effect of the same mutation in II:2?

AA of DC generally does not respond to IS

II:2 Unsuitable as marrow donor
**WHAT NEW (and old) test we should aim to**

<table>
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<tr>
<th>Test</th>
<th>Usefulness</th>
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| Chromosomal fragility test (MMC or DEB)   | • Mandatory in the diagnostic work-up of AA.  
  • Detects FA patients with mild /negative somatic phenotype.  
  • Addresses treatment (no IST in FA) and conditioning pre-HSCT (lighter in FA). |
| Mutation analysis of TERC and TERT (TNF2) genes | • Detects concealed forms of AD DKC  
  • 1-10% of AA pts carry these mutations |
| Mutation analysis of TINF2, NHP2, NOP10, DKC1 genes | When the phenotype of DKC is recognizable |
| Mutation analysis of cMPL gene(CAMT)      | • Useful in differentiating AA vs CAMT in the first years of life  
  • Mandatory in neonatal Thrombocytopenia |
| Telomere length measurement              | • Screening when congenital forms are suspected.  
  • Mandatory if suspected Dyskeratosis Congenita.  
  • Not available in all Centres. Not routine yet  
  • Prognostic relevance in acquired forms? |
Patients with shorter telomere had higher chance to develop MDS/leukemia after IST

Short telomeres are associated to increased risk of relapse and of mortality after IST

Not in standard clinical practice yet
Introduction

What is new

Diagnosis

First line treatment
   HSCT
   IST

Second line treatment
   HSCT
   IST

Experimental treatments
First line treatment in age <50 yrs (some says < 60 if medically fit)

Conditioning regimen:

• CY 50mg/Kg/day x 4 days + ATG. < 30 yrs

• RIC
CY1200mg/m², Flud 120mg/m² + ATG or Campath. 30-50 yrs

• Source of cells BM. NO PB
• GVHD proph MTX + CSA
Locasiulli et al, SAAWP, Haematologica 2007

**Figure 1.** Actuarial survival of 2479 patients with acquired severe aplastic anemia according to whether their first-line treatment was BMT or immunosuppression: the 10-year survival is 73% in BMT recipients and 68% in those treated with immunosuppression (p=0.002).
HLA id SIBILINGS 1999-2009: 10 years OS stratified according to stem cell source: BM vs PB

BM 88%

PB = 74%

P < 0.00001

Bacigalupo A et al SAAWP, Haematologica, 2012 in press
In whom

- Transfusion dependent NSAA
- SAA < 50 years old who lack an HLA identical sibling
- SAA > 50 years old (some say >60 yrs if medically unfit for HSCT)

Suggested scheme

1. Horse ATG (Atgam®), 40 mg/Kg i.v. in a 12-18h infusion, for 4 days (d 1-4)

2. CSA 5 mg/kg/day orally from day 5 to day +365. Than slow taper off.

3. Methylprednisolone for preventing serum sickness

4. G-CSF (lenograstim or filgrastim) 5 μg/kg/day continuously during the first 30 days. Afterwards during febrile or infectious episodes when ANC < 0.5x10^9/L.
Figure 2. Kaplan–Meier Curves of Overall Survival.
Panel A shows survival when data on patients were censored at the time of stem-cell transplantation; Panel B shows survival when stem-cell transplantation events were ignored.
rATG vs H ATG. SAAWP EBMT STUDY

Overall Survival  all AA  
(NSAA,SAA,VSAA)

Overall survival SAA

Horse ATG; n=105 86%  
Rabbit ATG; n=35 68%  
P=0.009

Horse ATG; n=67 91%  
Rabbit ATG; n=26 73%  
P=0.01

Marsh J for SAAWP EBMT, 2012

Only if horse ATG is not available, rabbit ATG can be considered
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
G-CSF

• No difference in OS, EFS, Response, Mortality, Clonal disease

• Reduction of infections and hospitalization days

• Identifies responders: pts achieving PNM > $0.5 \times 10^9/l$ within first 30 days have better survival and higher chances of response

Tichelli A et al SAAWP EBMT, Blood 2011
HORSE
ATG
(ATGAM°)

PDN

CsA

first year

1st year

months

months

1st line is protocol
Contents

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• Second line treatments
  HSCT
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• Experimental treatments
• If IST upfront fails, what is second line-treatment?

HSCT from UD if age < 65 yrs. This is because:

• Better donor selection by high resolution HLA typing
• Better supportive care
• New conditioning regimens

Have remarkably improved the outcome!

*In younger age group equals MFD HSCT*
Figure 4. The effect of transplant era: patients are stratified by the median year of transplant (2004): a trend for improved survival is seen for transplants performed after 2004.
After having failed IST upfront

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

Kosaka Y et al., Blood 2008, feb 1; 111(3): 1054-9
The WPSAA currently recommends

- **FLU** 30 mg/m² x 4 d (-5 to -2)
- **CY** 30 mg/kg x 4 d (-5 to -2)
- **ATG** x 2 d (-2, -3)
- **TBI** (2Gy) on day -1 for patients aged >14yrs.
  Consider also for children sensitized after numerous blood transfusions.

- **Alemtuzumab** (very low incidence of chronic GVHD) can be considered as a substitute to **ATG** (Marsh J et al., Blood 2011)

**ATG** or **Alemtuzumab** prevent severe Ac and Chronic GVHD
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
1. Rabbit ATG 3.5 mg/Kg i.v. for 5 days

2. CSA 5 mg/kg/day orally from day 5 to day + 180.

3. G-CSF (lenograstim or filgrastim) 5 μg/kg/day from d 1-90.

Response 77%

• Now would omit long-term G-CSF

• Rabbit ATG in refractory patients 33% response and 60% 3yr surv.

Alemtuzumab in relapsing patients 56% response and 86% 3 yr surv
refractory patients 37% response and 83% 3 yr surv


Di Bona E et. al, Br J Haematol, 1999
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  • Second line- treatmets
    HSCT
    IST

  • Supportive treatment

  • Salvage
Transfusion Policy in Aplastic Anemia

- **Restrictive Transfusion 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
Further recommendations

- **Leukoreduced** blood products to prevent HLA alloimmunisation.

- **Irradiated** products to prevent transfusion associated GVHD (higher risk with ATG) and to reduce sensitization to HLA e non HLA Antigens from multiple transfusions. Until lympho $\geq 1.0 \times 10^9$/L.

- Granulocyte transfusions in case of **severe infections** to bridge the gap until neutrophil recovery.

- **Iron chelation.** Desferioxamine 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.
What is new

Diagnosis

- First line treatment
  HSCT
  IST
- Second line treatments
  HSCT
  IST
- Salvage treatments
• OS (3yrs) 38% (71 patients)

• Acute GVHD (II-IV) 20%

• Chronic GVHD15% limited, 18% extensive

• Infection (38%) and graft failure (32%). Major cause of death

• Pre-freezing total nucleated cell count > 3.9x10^7/kg enhanced survival (45%) and neutrophil recovery 58%.

de La Tour et al, EUROCORD/EBMT BBMT 2010
CORD BLOOD

• Engraftment 55% (single unit)

• Survival at 2 years 41%
  20% for patients aged > 40yr.

• Survival at 3 years was 83% in a smaller serie  Yoshimi A, BBMT, 2008

Japanese people have greater similarity of HLA types.

Many more Japanese recipients can find a suitable CB than other nationalities.
Survival/3

Cord Blood Transplantation in SAA

Median follow-up 35 months
3y probability of OS 38%

HAPLO HSCT

3y OS 37%

Ac GvHD 3-4 = 17%

MT Lupo Stanghellini, 2012 SAAWP EBMT
ALEMTUZUMAB

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

Expands the hematopoietic stem cell compartment acting on cMPL = TPO receptor expressed on early and late progenitors
TPO-Eltrombopag
Eltrombopag

- Response 41% in refractory patients.
- Normalization of tri-lineage hematopoiesis and cellularity in some cases
- Limited side effects, no fibrosis
- ORAL!

Dunbar C, ASH meeting 2
FUTURE DIRECTIONS

• Mortality ~ 45% in early 80’s

• Outcome dramatically improved over time with up to 90% cure rate.

• More than one pathogenic mechanism (immune attack, telomere deficiency, intrinsic defect of the stem cell pool), acting in combination at a time.

• Refine diagnostics to identify which mechanism is prevailing in whom.

• Aim to individually tailored treatment (HSCT, IST, Androgens, stem cell expansion).