Haematopoietic Stem Cell Transplantation

Severe Chronic Neutropenia

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Giannina Gaslini Children’s Hospital

No disclosures
### Severe Chronic Neutropenia

<table>
<thead>
<tr>
<th>Category</th>
<th>ANC Range</th>
</tr>
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<tbody>
<tr>
<td>MILD</td>
<td>1000-1500/mmc</td>
</tr>
<tr>
<td>MODERATE</td>
<td>500-1000/mmc</td>
</tr>
<tr>
<td>SEVERE</td>
<td>500-200/mmc</td>
</tr>
<tr>
<td>VERY SEVERE</td>
<td>&lt;200/mmc</td>
</tr>
</tbody>
</table>

Persistence above 6 months

Autoimmune Neutropenia
Idiopathic neutropenia
Alloimmune Neutropenia
Cyclic neutropenia
Severe congenital neutropenia
NP associated to extra hematological features

Severe congenital neutropenia
Severe congenital neutropenia
clinical and genetic heterogeneity

- Early detection in life
- G-CSF dependency
- Recurrent bacterial infection

- ELANE
- JAGN1
- WAS
- CDL40
- CXCR4
- WHIM
- HAX 1
- Ak2
- TAZ
- GFI 1
- WHIM
- GSD1b
- SDS
- VPS45
- Rab27
- p14
- GATA2
- TCIRG1

Endoplasmic reticulum
Mitochondrial proteins
Glucose homeostasis
Ribosomal proteins
Lysosomal function
Transcriptional factor
Marrow microenvironment
Unknown mutations

X-linked
Immune functions

Boztug and Klein, 2009
Severe congenital neutropenia

Infections, unusual sites, even lethal

Transformation to myelodysplasia or acute leukaemia
**SCN natural history**

**Risk to develop lethal infection**

Cumulative incidence of sepsis/death, SCNIR

- Overall risk 10% after 15 years on G-CSF
- Low risk 5%  (G-CSF < 8 mcg/kg/die)
- High risk 18%  (G-CSF > 8 mcg/kg/die)

**Italian Registry**

- 10% after 3 years on G-CSF

**SCNRF and Swedish cohorts**

- No deaths in G-CSF treated population

SCN management

G-CSF therapy

Main target: lowest dose to protect against infections (ANC values between 1000-5000/cmm)

Starting dose 5 ug/kg/day subcutaneously
Subsequent doses have to be adjusted individually

Median dose to achieve the target 7.3 ug/kg/day (SCNIR) and 9 ug/kg/day (French Neutropenia Registry)

Lehrnbecher T BJH 2002
Bonilla BHJ 2004 NEJM 1989
Fioredda F, Am J Hematol 2011

Donadieu J, Haematologica 2005
Welte K Sem Hematol 2006
SCN management

G-CSF therapy

- Responders: G-CSF up to 15 µg/kg/day
- Low responders: G-CSF 15-20 µg/kg/day
- Non responders: G-CSF >20 µg/kg/day
SCN natural history

Risk of MDS/acute leukaemia transformation

SCN is a premalignant disorder (MDS/AL)

“Costitutional” mutations (ELANE Gly185 Arg or GATA 2) confer more leukaemogenic potential

CSFR3 mutation correlates with transformation

Role of G-CSF

Germeshausen M. Blood 2007, Beekman R. Blood 2012
The greater the G-CSF dose the higher the transformation rate !!!

MDS/AL cumulative incidence

SCNIR

Low Risk 15% after 15 years of G-CSF therapy

High risk: 34% after 15 years of G-CSF therapy

Rosenberg PS, BJH 2010
MDS/AL cumulative incidence

SCFN

10.8% after 15 years of G-CSF therapy

Median dose of the whole cohort 9.4 mcg/kg/die
Median dose of MDS/LA 14 mcg/kg/die
G-CSF doses and duration

Donadieu J, Haematologica 2005
THE ONLY CURATIVE TREATMENT IS BONE MARROW TRANSPLANTATION
Indication to HSCT

**Absolute indication**
Non responders to G-CSF (ANC < 1 x 10^9/L or poor infection control with G-CSF doses > 20 mg/kg)
Before/early transformation to MDS/AL (morphology, cytogenetics)

**Debatable**
Low responder to G-CSF (G-CSF 15-20 mg/kg to achieve ANC >1 x 10^9/L and infection control)

Responders to G-CSF but at G-CSF dose between 8-15 mg/kg
CSFR3 mutated patients
Gly 185 Arg mutation in the ELANE gene

Not if alone
Type of Donor
TO TRANSPLANT OR NOT TO TRANSPLANT
THAT’S THE TROUBLE!!!
HSCT in SCN UP-TO-DATE

DATA FROM SMALL SERIES AND SHORT REPORTS

❖ HSCT outcome in SCN and differences between patients with or without transformation to MDS/AL
❖ Role of HLA match in HSCT outcome
❖ Source of stem cells
❖ Type of conditioning regimen
❖ GVDH occurrence and prophylaxis
❖ Transplant related mortality

Connelly et al Cur Op Hematol 2012
OUTCOMES OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR SEVERE CONGENITAL NEUTROPENIA (SCN)

On behalf of the Severe Aplastic Anemia, Pediatric Disease and Inborn Errors WPs of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT)
Aim of the study

Outcome of HSCT in a large cohort of 136 SCN patients

Identification of risk factors associated with the outcome

EBMT database: unique opportunity to address unanswered questions!!!
Patients and methods

Inclusion criteria
SCN diagnosed early in life
Bone marrow block at promyelocytes stage
G-CSF dependency

Data collection
General database (MED A and B forms)
Dedicated form (MED C form)

FORM C : Severe Congenital Neutropenia
Information about the disease
Patients ______ Date of birth ______

Marrow morphology at dx: maturing block at myelocytes or promyelocytes
Mutation associated to neutropenia:
ELANE, HAX1, GFI1, G6PC3, GATA2, CXCR4, WASP, SDS, SSD1b, OTHER.
Not done Not found any known

CSF3 mutation
Y ☐ N ☐ Date ______
Type __________________

Median ANC the year before HSCT ______/mmc
Any extrahaematological features N ☐ Y ☐ if yes type ______

Treatment before HSCT
G-CSF Y ☐ N ☐ Median G-CSF dose/kg
Daily
Every other day
Less frequently than every other day

Significant change in dose needed during the history of the disease
Y ☐ N ☐

Quantification of increase/decrease of G-CSF dose 25-50%, 75-100% ______

Other treatment Y ☐ N ☐ Type of treatment

Documented Infections during G-CSF treatment:
Skin, subcutaneous, mouth abscesses, otitis, pneumonia, Osteomyelitis, meningitis, deep infections (involving bone etc.), sepsis, other specify ______ (Tick/circle what interests. Even more than one option is acceptable)

Episodes/year Hospitalization Y ☐ N ☐

Additional information
Marrow at HSCT Y ☐ N ☐
Morphological MDS feature Y ☐ N ☐
Leukemia Y ☐ N ☐
Chromosome aberration Y ☐ N ☐

Notes __________________________
### Characteristic of the cohort

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<td>Male</td>
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<td>50</td>
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<td>Patients origin</td>
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<td>United Kingdom</td>
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<td>16</td>
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<td>France</td>
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<td>9</td>
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<td>Germany</td>
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<td>Italy</td>
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<td>Saudi Arabia</td>
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<td>Nederlands</td>
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<td>Poland</td>
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<td>Spain</td>
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<td>Austria, Russia, Ireland, Australia, Switzerland, Greece, Iran</td>
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<td>Median age at diagnosis</td>
<td>0.4 years (0-35.5)</td>
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<td>Median age at first HSCT</td>
<td>4.7 years (0.22-43.09)</td>
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<td>Median follow up after HSCT</td>
<td>55 months (9.4-98)</td>
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<td>Disease phenotype</td>
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<td><strong>Molecular Mutation</strong></td>
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<td>ELANE</td>
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<td>G6PC3</td>
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<td>No mutation</td>
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<td><strong>G-CSF before HSCT</strong></td>
<td>100</td>
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<td>Yes</td>
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<tr>
<td>G-CSF &gt; 5 mcg/kg</td>
<td>78</td>
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<td><strong>Infections prior HSCT</strong></td>
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<td>Noone</td>
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<tr>
<td>Sub/cutaneous</td>
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<td>Respiratory</td>
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<td>Deep/systemic</td>
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<td><strong>Hospitalization</strong></td>
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<tr>
<td>No</td>
<td>16</td>
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<tr>
<td><strong>AL/MDS at HCST</strong></td>
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<tr>
<td>yes</td>
<td>16</td>
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<tr>
<td>no</td>
<td>84</td>
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<tr>
<td><strong>Median ANC 1 yr before HSCT</strong></td>
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<tr>
<td>&lt;500/cmm</td>
<td>73</td>
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<tr>
<td>500-1000</td>
<td>15</td>
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<tr>
<td>&gt;1000</td>
<td>12</td>
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## Data on HSCT

<table>
<thead>
<tr>
<th></th>
<th>%</th>
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<tbody>
<tr>
<td>HCST type</td>
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<tr>
<td>Matched related donor</td>
<td>45</td>
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<tr>
<td>Matched unrelated donor</td>
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<tr>
<td>Mismatched donor</td>
<td>10</td>
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<tr>
<td>Stem Cell Source</td>
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</tr>
<tr>
<td>Bone Marrow</td>
<td>58</td>
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<tr>
<td>Peripheral blood</td>
<td>24</td>
</tr>
<tr>
<td>Cord Blood</td>
<td>18</td>
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<tr>
<td>Conditioning regimen</td>
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</tr>
<tr>
<td>Myeloablative</td>
<td>92</td>
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<tr>
<td>Reduced Intensity</td>
<td>8</td>
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<tr>
<td>GVDH Prophylaxis</td>
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</tr>
<tr>
<td>Cyclosporin</td>
<td>58</td>
</tr>
<tr>
<td>Cyclosporin+Methotrexate</td>
<td>42</td>
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<tr>
<td>Fludarabine</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
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<tr>
<td>No</td>
<td>58</td>
</tr>
</tbody>
</table>
Overall Survival

3 years 82%
Event free survival

3 years
71%
Causes of death

Deaths 25/136 (18%)

GVDH 8/25 (32%)
Infections 5/25 (20%)
Organ failure 4/25 (16%)
Relapse/progression disease 2/25 (8%)
Others 6/25 (24%)

TRM 17% !!!!
OS by age

p = 0.0162
OS by period

p = 0.02
OS by HLA match

- HLA matched
- Mismatched

p = 0.001

- HLA matched related
- HLA matched unrelated
- Mismatched

p = 0.049
OS by source of cells

\[ p = 0.12 \]
OS by AL/MDS yes/no

- No: 73, 56, 48, 42, 32, 26, 20, 15, 13, 9, 6
- Yes: 14, 13, 11, 9, 9, 7, 7, 6, 5, 3

p = 0.72
OS by conditioning type

p = 0.3

**indications:** 4 non response, 1 bone marrow failure, 4 MDS “fully or partially refractory to G-CSF”: no ANC increase with G-CSF ≥ 50 mg/Kg

6/9 pts are alive and in CR with a median follow up of 3.1 yrs

*OS by GVDH prophylaxis*

HSCT is feasible for SCN pts who do not respond to G-CSF, have malignant transformation, are at high risk of transformation even if an HLA-id sibling donor is not available

\[ p = 0.03 \]
Engraftment

Engraftment 91%
Primary graft failure 6%
Secondary graft failure 3%

Outcome of patients with graft failure

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<thead>
<tr>
<th>Alive</th>
<th>Dead</th>
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<tbody>
<tr>
<td>42%</td>
<td>58%</td>
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</table>

No impact of any risks factor on graft including use of RIC vs myeloblative conditioning regimen
Acute GVDH

<table>
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<tr>
<th>Grade</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>I-II</td>
<td>32</td>
</tr>
<tr>
<td>III-IV</td>
<td>15</td>
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</table>

\[ p = 0.006 \]
Significant more cGVDH in patients older than 10y
Retrospective study based on data reported to Eurocord Registry about patients with hereditary BM failure syndrome who underwent CBT.

Dx: DBA 21, CAMT 16, DC 8, SDS 2, SCN 16, unclassified 1

Rel 20: 19/20 HLA matched sibling

Unrel 44: 86% mismatched, 3 had 2 UCBUs

TNC 5x10^7/Kg 6.1x10^7/Kg

N recovery cumulative at 60 days 95% 55%

aGvHD grade II-IV 2 pts 2 yrs cumulative 24%

cGvHD 2 yrs cumulative incidence 11% 53%

3 year OS: 95% 61% (better OS with age 5 yrs and TNC ≥ 6.1x10^7/Kg)

-Related UCBT is associated with excellent outcome

- Increasing cell dose and better HLA matching might provide better results in unrelated CBT

p = 0.006
TAKE HOME MESSAGES (1)

HSCT safe option in G-CSF poor responders and in MDS/AL transformed pts

Better results at age younger than 10 years

Non negligible TRM 17%

Good OS and EFs good both with related or unrelated donors

No difference in OS and EFS both for patients with and without leukaemia
TAKE HOME MESSAGES (2)

Bone marrow and cord blood do better than peripheral blood because of risk of cGVDH,

Significantly better survival in CsA and MTX association compared to CsA alone group

RIC is promising because no difference in engraftment has been shown compared with MyA

No late effects reported....short follow-up
THANK YOU!!