RESULTS OF HSCT FOR DYSKERATOSIS CONGENITA AND FANCONI ANEMIA

Carlo Dufour, MD
X linked, Autosomal Dominant and Autosomal Recessive

Approx 50% of patients have mutations in 6 telomerase-sheletrin genes

DKC1 (36%)
TNF2 (11%)
TERC (6%)
TERT (1%)
NOLA2 (<1%)
NOLA 3 (<1%)

DC Registry

Very short telomere
CLINICAL PHENOTYPE

- TRIAD
  - Reticular Skin Pigmentation
  - Abnormal nails
  - Leuko/Erythroplakia

  plus variable combination of
  - Pulmonary fibrosis
  - Marrow failure
  - Immunodeficiency (T & B)
  - Somatic malformations  (epihora, blepharitis, delayed development)
  - Cancer susceptibility  (MDS; leukemia, epithelial K).

   Instituto Giovanni Gaslini
Clinical TRIAD

Skin

Nails

Mucous membranes
TRIAD plus variable combination of

- Pulmonary fibrosis
- Marrow failure
- Immunodeficiency (T & B)
- Somatic malformations (epihora, blepharitis, delayed development)
- Cancer susceptibility (HNSCC, Anorectal, Skin, Leukemia)
Two forms have a very severe phenotypes

1. Hoyeraal- Hreidarsson Syndrome (HH) (DKC1, NF2 & TERT)
   Cerebellar hypoplasia

2. Revesz Syndrome (RS) (TNF2)
   Bilateral exudative retinopathy and CNS calcifications

Disease anticipation i.e. 1-2 decades earlier in new generations.
More often in AD forms (TERC, TNF2, TERT).

Investigate relatives at diagnosis also if asymptomatic
14 yr old boy

WBC 2.7 x10⁹/l, ANC x1.0⁹/l, Hb 14 g/dl, Plts 73 x10⁹/l

Hypocellular marrow

Non SAA

No transfusions
Results in a nucleotidic change in CR1, a highly conserved region, which functions as a template for the telomeric DNA synthesis. Does not alter RNA structure.

But changes the telomeric sequence

\[
\text{wt: TTAGGG} \quad \text{TGTGGG}
\]

AA and TERC mutation
TERC c53 T>A FAMILY

- **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
50 - 60% of cases.

2nd decade of life.

Later – 3rd-4th decade -- often with NO mucocutaneous abnormalities in AD forms
Increased risk of toxicity (limited restorative ability of tissue damage due to telomere maintainance failure).

Difficult to find a related donor
- genetic disease
- silent carrier in the family

Very few studies in literature. All small sized. Some review
HSCT in LITERATURE

OS in 65 pts from literature

Sib 71%
Alt 31%

Sib 69%
Alt 29%

OS 11 pts from NCI

9/30 deaths Pulmonary fibrosis

3 +11 reviewed =14 pts. age 2-29 yrs

Alive 8
5/8 Reduced Intensity

Deaths 6
All Myeloablative or TBI

Alter et al, Blood 2009

Nishio N. et al Pediatr Transplantation, 2010
EMBT Study
PI Elizabeth Korthof

- Data from EBMT data base & personal contacts: n=44.
- Data from the literature: n=47.
  (Authors were asked for additional data)
- Total 91 patients.
- The largest study ever conducted on HSCT in DC.
- Still some data to acquire.
<table>
<thead>
<tr>
<th>PATIENT &amp; HSCT CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 63, Females 22, Unkn 6</td>
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<tr>
<td>Donor (84/91 pts)</td>
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<tr>
<td>ID SIB 44%</td>
</tr>
<tr>
<td>MUD 26%</td>
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<tr>
<td>Altern 30%</td>
</tr>
<tr>
<td>Conditioning (72/91 pts)</td>
</tr>
<tr>
<td>Myeloabl 51%</td>
</tr>
<tr>
<td>NON Myeloabl 49%</td>
</tr>
<tr>
<td>Cell source (84/91 pts)</td>
</tr>
<tr>
<td>BM 78%</td>
</tr>
<tr>
<td>CB 13%</td>
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<tr>
<td>PB 9%</td>
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<tr>
<td>GvHD proph (71/91 pts)</td>
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<tr>
<td>CsA in comb 70%</td>
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<tr>
<td>CsA mono 20%</td>
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<tr>
<td>Other 10%</td>
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</table>
HSCT RESULTS

Post HSCT Follow-up
survivors 3 yrs
all pts 0.7 yr

Engraftment (78/91 pts)
Yes 91%
No 9%

Ac GVHD (60/91 pts)
no-I 68%
II-IV 32%

Ch GVHD too many missing data

Survival (88/91 pts)
Deceased 51%
Alive 49%

Causes of Death (27/45 pts)
TRM 74%  Infection, Rejection, organ Tox, Interst Pneum.
DC related 26%  Pneumonia, Pumomary fibrosis, Late MOF, Malignancy
Overall survival

Survival Function

Cum Survival

intervalSCT1date last seen days

Probability

Days

Institute Giornina Castori
Other data

- Late Malignancy 3 (1.2 - 11.7 yr after 1 sct)
- Pulmonary fibrosis: 4 after SCT1, 2/8 after SCT2
- In univariate analysis no variable impacted on survival. MV n.a.
TAKE HOME MESSAGE

- Overall survival 50% after 8.2 years. No plateau.
- TRM major cause of death, more than DC related.
- Engraftment not a problem.
- Post HSCT Lung problems.
- RIC. If TBI, side to side, arms resting laterally.
- Malignancy occurrence ~ 7%. Rather early vs non HSCT pts (literature).
FANCONI ANEMIA

- AUTOSOMIC-RECESSIVE and X-LINKED DISEASE
  Wide clinical-biological heterogeneity

- Ca 1500 cases described in literature. M/F ratio = 1.3/1

- Incidence: ≅ 3 cases/million newborn/year

- Prevalence: 1-5/million.

- Heterozygous frequency
  1:300 (USA - Western Europe)
  1:100 (South - Africa)
Distribution of defective genes among patients

Auerbach A. Fanconi Anemia Database

Novel genes (FAAP20, RAD51C, DDX11, SLX4) to be included
CLINICAL PHENOTYPE

- Somatic abnormalities
- Cancer susceptibility
- Progressive bone marrow failure
- Increased chromosome fragility
MARROW FAILURE

• Between the age of 5 and 10 years.

• Cytogenetic clone in ~ 30% of patients.

• Head, cardiac, renal malformations and hearing impairment increase the risk.

• Absent/anomalies radii increase the risk too

P Rosenberg for the German Fanconi Anemia Registry, Haematologica 2008
RESULTS of HSCT

• Overview on all HSCT

• Matched sibling donor
  Irradiation
  No Irradiation

• Matched Unrelated donor
  The FLU „ERA“
  Irradiation
  No Irradiation

Institute Giammina Gastone
Allogeneic SCT for FA All HSCT

Overall Survival

Median fup: 63 months

N=923 → 839 first SCT included

1972- 2009

65% Matched related donor

Deaths: n=294

- GvHD, n=102
- Infections, n=79
- Graft rejection: n=47

64% (95%CI 60-67) at 5 y
60% (95%CI 56-64) at 10 y

Overall survival

No. at risk

839 462 354 271 203 156 130

Time (months)
<table>
<thead>
<tr>
<th></th>
<th>Dufour et al. BJH 2001</th>
<th>Farzin et al BJH 2007</th>
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<tbody>
<tr>
<td>Nº of Patients</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Conditioning Regimen</td>
<td>TAI/TBI 500 cGy</td>
<td>TAI/TBI 400cGy</td>
</tr>
<tr>
<td></td>
<td>+LD CY</td>
<td>+LDCY</td>
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<tr>
<td></td>
<td>HD CY</td>
<td>ATG</td>
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<tr>
<td>Graft failure</td>
<td>8%</td>
<td>5.7%</td>
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<tr>
<td>Ac GVHD ≥grade 2</td>
<td>36%</td>
<td>14.2%</td>
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<tr>
<td>C GVHD</td>
<td>12.5%</td>
<td>12%</td>
</tr>
<tr>
<td>TRM</td>
<td>18.5%</td>
<td>8.5%</td>
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<tr>
<td>Late Tumours</td>
<td>0</td>
<td>5.7%</td>
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<tr>
<td>Follow-up</td>
<td>3 yrs</td>
<td>10 yrs</td>
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<tr>
<td>Over. Survival</td>
<td>81.5%</td>
<td>83%</td>
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<td>-------------------------</td>
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<tr>
<td>Patient N°</td>
<td>11</td>
<td>34</td>
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<tr>
<td>Conditioning Regimen</td>
<td>CY 20+ FLU + ATG pre TCD</td>
<td>Cy 60 + ATG</td>
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<tr>
<td>Graft failure</td>
<td>9%</td>
<td>0%</td>
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<tr>
<td>Ac GVHD</td>
<td>0 %</td>
<td>17</td>
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<tr>
<td>≥grade 2</td>
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<tr>
<td>C GVHD</td>
<td>0 %</td>
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<tr>
<td>TRM</td>
<td>9%</td>
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<tr>
<td>Late Tumours</td>
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<tr>
<td>Follow-up</td>
<td>2.9 yrs</td>
<td>2.9 yrs</td>
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<tr>
<td>Over. Survival</td>
<td>100%</td>
<td>97%</td>
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<tr>
<td>EFS</td>
<td>82%</td>
<td>82%</td>
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IRRADIATION vs NON IRRADIATION
in HLA MSD

Comparative analysis of 148 pts (71 non-rradiation vs 77 yes irradiation)

No differences in Engraftment
  Ac GVHD,
  CGVHD
  TRM
  OS (79% vs 81%) fup > 5 yrs

Higher mortality > 10 yrs age
  and CMV pos (either donor or recipient) in both irradiation and non irradiation group

R Pasquini BBMT for CIBMTR 2008
Allogeneic SCT for FA. ALL HSCT

Overall Survival

1972-2000

2001-2009

Period effect P<0.0001

Regis Peffault de la Tour et al.

Preliminary Results
<table>
<thead>
<tr>
<th>Condition</th>
<th>Flu (53%) vs Non-Flu (13%)</th>
<th>Flu (24%) vs Non-Flu (65%)</th>
<th>Flu (89%) vs Non-Flu (69%)</th>
<th>Overall (29%)</th>
<th>Non-Flu (21%) vs Non-Flu (70%)</th>
<th>Flu (16%) vs Non-Flu (Non T cell depl)</th>
<th>Other (31%)</th>
<th>Flu (47%) vs Non-Flu (81%)</th>
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<tbody>
<tr>
<td>Survival</td>
<td></td>
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<td>Early Mortality</td>
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<tr>
<td>Engraftment (PMN)</td>
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<tr>
<td>Ac GVHD II-IV</td>
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<tr>
<td>C GVHD</td>
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<td>TRM</td>
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Overcome the negative effect of mosaicism on rejection

J Wagner et al, Blood 2007
ALTERNATIVE DONOR - IRRADIATION

- **TBI 300**  - Th Sh-, Cy 40 mg, FLu 140, ATG 150 mg/kg, TCD, CsA
  - 24 pts
  - OS 86%
  - Short FUP
  - Ac GVHD II-IV 23%
  - C GVHD no

  M Mc Millan BBMT 2009

- **TBI 450**  - Cy 40 mg, Flu 150, rATG 10 mg/kg, TCD, Tacrolimus
  - 21 pts
  - OS 72%
  - at 5 yrs
  - Ac GVHD II-III 5.5%
  - C GVHD 5.5%

  Chaudhury Br J Haematol 2008

- **TBI 300-450**  - Cy 40 mg, FLu 150-180, ATG, Tacrolimus
  - 27 pts
  - OS 96%
  - at 3.1 yrs
  - Ac GVHD II-IV 11%
  - C GVHD 30%

  Yabe et al Br J Haematol 2006
ALTERNATIVE DONOR - NO IRRADIATION

- Cy 60 mg/Kg, FLU 125 mg, rATG 4 mg/kg, CsA
  60 pts
  
  OS 53.5% 5 yr f-up
  (<10 yrs OS 92%, > 10 yrs 53%)
  OS for 8/8 matched 81% at 3 yrs
  
  Tongue carcinoma in 10 pts, 7/10 with GVHD

- Cy 20-30 mg/Kg, Flu 125 mg, ATG 37.5 mg/kg
  7 pts
  
  7/7 alive at median 3 yrs f-up
  Ac GVHD II-III 71%
  C GVHD 28%

C Bonfim 2010

Motwani BMT 2005
93 transplants. 12 HLA identical, 81 NON HLA identical

OS 40%
(3 yrs prob) 53% (with Flu) vs 19% (non Flu)
Ac GVHD II-IV 32%
C GVHD 16% ca
TRM 59%

E. Gluckman, BBMT 2007
MISMatchED  FAMILY & HAPLO DONOR

EBMT SAAWP retrospective analysis of 43 pts
17 true Haplo
26 >1Ag MM family donors

No diff in -A & cGVHD - TRM

Causes of Death (>1)
Infections
Graft Failure
GVHD

MULTIVARIATE ANALYSIS
• Transplant at age < 9 yrs significantly better survival (p 0.0001).
• Flu & NO irradiation trend to better survival.

E. Korthof 2010
Approx 40% develops tumours 15-20 yrs after SCT.

Transplanted patients have higher and earlier occurrence of tumours over NON transplanted patients.

G Sociè, Blood 2005

- Intrinsic tendency to develop tumours.

- Head & Neck SCC may occur earlier, ~ 8 years after SCT with TAI & CY and in pts suffering from GVDH.

P Rosenberg, Blood, 2005
ALTERNATIVE DONOR TRANSPLANTS

- Survival is improving peaking to MDS rates.
- Flu very beneficial.
- TRM and GVHD still a problem (> in no irradiation).
- Irradiation vs no irradiation: still unresolved issue. Probably cautious to avoid irradiation in NON MDS/LA pts
- If no matched donor, MM family and Haplo can be considered. Use Flu
Monitoring plan. Relatives testing for FA and compatibility

**DIAGNOSIS**

- HLA identical FAMILY DONOR
  - yes
  - HSC TRANSPLANT With Flu containing RIC before TS
    - Or
    - PLT <40x10^9 / L
    - HB < 9 gr/dl
    - PMN 1-0.5 x 10^9/ L
    - Or
    - Persistent Cytog Clone
    - Abn chr 7, 3,1
    - MDS, AML

- no
  - Serch for unrelated donor
    - HLA id donor found
    - HSC TRANSPLANT With Flu containing RIC before TS
      - Or
      - PLT <30x10^9 / L
      - HB < 9 gr/dl
      - PMN 1-0.5 x 10^9/ L
      - Or
      - Persistent Cytog Clone
      - Abn chr 7, 3,1
      - MDS, AML
    - Donor not found
      - Androgens + Steroids
      - Experimental treatment anti TNF α gene therapy
      - In vitro FERTILIZATION and embrio selection

MM family/Haplo donor
• **Mini Flag** (Flu 30 mg/m², ARA-C 300 mg/m² days -2-4) pre HSCT is well tolerated
  (Cincinnati).

• NO previous cytoreduction but **directly** to HSCT with
  TBI 300 (TH SH), Cy 40 mg, FLu 140, ATG 150 mg/kg, TCD, CsA.
  (Minneapolis)
Graft failure ~10% in both matched sibling and alternative donor SCTs
If in need of a second SCT use the same donor or change the donor?

Retrospective study EBMT-Brasil-Curitiba on 106 FA pts

Changing the donor after failure of first graft does not affect survival

Trend to better surv with DD after 1ry graft failure

E Korthof, C Bonfim, C Dufour 2010