CURRENT MANAGEMENT APPROACHES FOR MYELODYSPLASTIC SYNDROMES (MDS)

Bone Marrow Failure in MDS: Role of Abnormal Telomere Dynamics

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Direction, Trans-NIH Center for Human Immunology, Autoimmunity, and Inflammation

American Society of Hematology, Atlanta, December 7, 2012
"For unknown reasons, a ‘weakness’ may occur in specific chromosomes with respect to control of mitosis that at first remains latent and thus is transmitted to a large number for daughter cells. . . . With the beginning of senescence, perhaps this latent weakness becomes manifest in the failure of mitotic control in such a way that when cell division occurs, there is a possibility of generating daughter cells with recurrent abnormalities."
AA AND MDS

Clonal evolution in practice (AA, FA, SBDS, DKC)

Diagnostic confusion by pathology

Shared pathophysiology and responses to treatment

CLONAL EVOLUTION AND TELOMERE ATTRITION

Telomere biology

Human telomeropathy and organ failure

Telomere attrition and cancer

Therapeutic opportunities
CANCER RISK IN DKC

literature survey

NCI cohort

Alter BP et al 2009; 113:6549
### A RANDOMIZED TRIAL OF H-ATG VS. R-ATG IN SAA

**HEMATOLOGIC RESPONSES AT 3 AND 6 MONTHS**

<table>
<thead>
<tr>
<th></th>
<th>Horse ATG</th>
<th>Rabbit ATG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3 months</strong></td>
<td>37/60 (62%)</td>
<td>20/60 (33%)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td>41/60 (68%)</td>
<td>22/60 (37%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

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**Survival Analysis**

- **1996-2002**
  - 5-yr survival = 91%
- **2002-2008**
  - 5-yr survival = 94%
- **1989-1996**
  - 5-yr survival = 92%

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Scheinberg P et al NEJM 2011; 365:430
Valdez JM et al, Clin Inf Dis 2011; 52:726
CLONAL EVOLUTION IN SEVERE APLASTIC ANEMIA

>300 pts treated since 2000 AT NIH Clinical Center on horse ATG regimens

Median time to evolution = 613 day (IQR 208-977; range 171-2725)

Scheinberg P and Young NS, Blood 2012; 120:1185
AA or MDS?
CLINICAL ASSOCIATIONS BETWEEN MDS AND AUTOIMMUNE DISEASE

Table 1  Inflammatory Diseases Associated with MDS

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute febrile neutrophilic dermatosis (Sweet’s syndrome)</td>
</tr>
<tr>
<td>Allergic granulomatosis</td>
</tr>
<tr>
<td>Behçet’s syndrome</td>
</tr>
<tr>
<td>Chronic nonsuppurative panniculitis</td>
</tr>
<tr>
<td>Cutaneous vasculitis</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonitis</td>
</tr>
<tr>
<td>Eosinophilic fasciitis</td>
</tr>
<tr>
<td>Erythema elevatum diutinum</td>
</tr>
<tr>
<td>Erythema nodosum</td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
</tr>
<tr>
<td>Subcorneal pustular dermatosis</td>
</tr>
</tbody>
</table>

Hamblin TJ 2002, in Bennett JM, The Myelodysplastic Syndromes (Marcel Dekker, New York, page 65)

Table 1  Immunological manifestations in myelodysplastic syndromes patients

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Serological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute systemic or skin vasculitis</td>
<td>Direct Coombs’ test positivity</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Hypergammaglobulinaemia</td>
</tr>
<tr>
<td>Autoimmune cytopenias</td>
<td>Hypogammaglobulinaemia</td>
</tr>
<tr>
<td>Colonic ulcerations</td>
<td>Monoclonal parproteinaemia</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Positivity for autoantibodies</td>
</tr>
<tr>
<td>Peripheral polyneuropathy</td>
<td></td>
</tr>
<tr>
<td>Polychondritis</td>
<td></td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td></td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
</tbody>
</table>

SPONTANEOUS PRODUCTION OF TNF BY MARROW MONONUCLEAR CELLS

TNF-α, pg/mL/2 x 10^6

MDS  AA  Normal
OLIGOCLONAL T CELL EXPANSION IN TRISOMY 8 MDS

Vβ-Subfamily Analysis by Flow Cytometry

Percent

Vβ-subfamily

trisomy 8 patient

trisomy 8

normal

0 5 10 15 20 25 30 35

normal

14 2 17 3 5.1 7 14.2 17 3 5.1 7
## CLINICAL TRIALS OF ATG FOR CYTOPENIAS IN MDS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Median Age</th>
<th>Overall Response</th>
<th>Response in RA</th>
<th>Median Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>129</td>
<td>60</td>
<td>30%</td>
<td>40%</td>
<td>&gt;44 mos</td>
</tr>
<tr>
<td>London</td>
<td>30</td>
<td>55</td>
<td>50</td>
<td>62</td>
<td>16</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>31</td>
<td>59</td>
<td>16</td>
<td>11</td>
<td>12-60</td>
</tr>
<tr>
<td>Hannover</td>
<td>35</td>
<td>63</td>
<td>34</td>
<td>42</td>
<td>&gt;9</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>8</td>
<td>69</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Karolinska</td>
<td>20</td>
<td>64</td>
<td>30</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Manchester</td>
<td>13</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>Dusseldorf</td>
<td>9</td>
<td>59</td>
<td>33</td>
<td>16</td>
<td>57</td>
</tr>
<tr>
<td>UK</td>
<td>96</td>
<td>55</td>
<td>42</td>
<td>--</td>
<td>32</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>371</strong></td>
<td></td>
<td><strong>34%</strong></td>
<td><strong>44%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Sloand EM, Rezvani K, Sem Hematol 2008; 45:39
CAMPATH FOR LOW RISK MDS

N = 28; Int-1; selected for response criteria (age, HLA-DR15, tx history)
Alemtuzumab: 10 mg/d intravenously x 10 days
Primary endpoint: hematologic status at 3 months

Individual Patient Responses

Sloand EM et al, J Clin Oncol 2010; 28:5166
# CYTOGENETIC RESPONSES TO CAMPATH IN MDS

<table>
<thead>
<tr>
<th>UPN</th>
<th>Pre-treatment</th>
<th>6 mo post-treatment</th>
<th>1 year post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>47, XY+8</td>
<td>47, XY+8</td>
<td>46xy (20)*</td>
</tr>
<tr>
<td>7</td>
<td>46.XX, t(3;8)(q26.1;q22),del(13)(q12q22)[7] / 46.XX[13]</td>
<td>46, XX, t (3;8) (q26.1; q22), del(13) (q12q22) [1] / 46, XX [19]</td>
<td>46XX (20)*</td>
</tr>
<tr>
<td>14</td>
<td>46, XY, del(7)(q22q36)[9]/46,XY[3]</td>
<td>46xy (20)*</td>
<td>46xy (20)*</td>
</tr>
</tbody>
</table>

* Verified by FISH
Bone marrow failure syndromes

- SDS
- DKC
- AA
- PNH
- AML
- LGL

Autoimmune disease: MS, IBD, uveitis, DM type 1, etc.

Hypocellular MDS

Myelodysplastic syndromes
THE PROBLEM OF CLONALITY IN BM FAILURE DISEASES

Clinical similarity and nosologic confusion

Modern “natural history” of marrow failure with treatment and support

Fanconi anemia, Schwachman-Diamond, and dyskeratois congenita
Evolution of SAA to MDS/AML post-IST
Telomeropathies
The problem of clonality is a problem with DNA

- Free ends of linear chromosomes must be different from damaged DNA fragments. (H Muller, B McClintock, 1930-40s)

- If DNA polymerase binds to only a single strand, how can DNA fully replicate? (A Olovnikov, J Watson, 1970s)
TELOMERE STRUCTURE

Calado RT, Young NS, N Engl J Med 2009; 361:2353
TELOMERASE ELONGATES THE 3’ END OF TELOMERES BY ADDING TTAGGG REPEATS

Telomeric repeats added by telomerase (each band in ladder varies in 6 nucleotides in length)

Internal control

RNA component

CR4-5

HACA (CR6/CR8)

(CR2/CR3) Core Pseudoknot

Template

5’

Dyskerin

NHP2

NOP10

(CR7)

GAR

RNA template

Telomerase

GGGTTAGGGTTAGGG

TTAGGG-3’

CCCAATCCC-5’

AAUCCC

Telomere

N-Terminal Region

Reverse-Transcriptase motifs

C-Terminal Region

Telomerase reverse transcriptase

N

TEN

CP

QFP

T

1

2

A

B

CD

E

E-I

E-II

E-III

E-IV

C’ 1132 aa

Telomerase Activity

primary
cells

Negative control

Positive control
CONSEQUENCES OF TELOMERE EROSION

Chromosomal Instability

Senescence/
Apoptosis
(Hayflick phenomenon)

↑p53
DYSKERATOSIS CONGENITA

X-linked DKC

DKC1 (encoding dyskerin, protein component of telomerase complex)

Autosomal Dominant DKC

TERC, RNA component of telomerase
TINF2 (shelterin protein)
RTEL1 (DNA helicase)

Autosomal Recessive DKC

TERT, NOP10, NHP2, WRAP3

leukoplakia

nail dystrophy

hyperpigmentation

Courtesy by B. Alter, NCI
LATE PRESENTATION OF DYSKERATOSIS CONGENITA

37 y/o US Army officer in Afghanistan tongue ulcer, diagnosed as squamous cell carcinoma single round of chemotherapy and radiation resulted in unexpected extreme, persistent pancytopenia/ Later, pulmonary metastases novel Val329Gly mutation in \textit{DKC1}
TELOMERE LENGTH IN TERT MUTATION LEUCOCYTES

Mutations in TERT, the Gene for Telomerase Reverse Transcriptase, in Aplastic Anemia

Tedri Yamaguchi, M.D., Rodrigo T. Calado, M.D., Ph.D., Hinh Ly, Ph.D., Sachiko Kajigaya, Ph.D., Gabriela M. Becker, M.D., Stephen J. Chanock, M.D., Peter M. Lansdorp, M.D., Ph.D., and Neal S. Young, M.D.
32 y/o male pipe-fitter from Wisconsin chronic progressive thrombocytopenia x 9 yrs negative family history mildly elevated MCV gray hair from his early 20s cryptic cirrhosis
TERT S368F
(adjacent to VSR motif)

- thrombocytopenia, "malignant histiocytosis"
- pulmonary fibrosis, cirrhosis
- bicytopenia, portal sclerosis
- short telomeres
- aplastic anemia
- bicytopenia, portal sclerosis
- aplastic anemia, cirrhosis

A New Syndrome of Familial Aplastic Anemia and Chronic Liver Disease
HEMATOLOGY/HEMATOPOIESIS IN FAMILY MEMBERS

Hematology
- normal peripheral blood counts
- mild anemia with macrocytosis
- mild thrombocytopenia

Hematopoiesis
- severely hypoplastic
- ↓CD34 number
- ↓colony formation
- ↑erythropoietin, thrombopoietin

proband
affected sister
affected niece
unaffected brother
DELAYED ENGRAFTMENT AND DONOR-DERIVED LEUKEMIA AFTER TRANSPLANTATION OF UMBILICAL CORD BLOOD WITH EXTREMELY SHORT TELOMERE LENGTH

<table>
<thead>
<tr>
<th>Samples</th>
<th>Telomere length (kb)</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB0 Pre-Trasplant</td>
<td>4.781085436</td>
<td></td>
</tr>
<tr>
<td>CB1 Sample before transplant</td>
<td>7.75451172</td>
<td>4.1 below</td>
</tr>
<tr>
<td>CB2 Sample after engraftment</td>
<td>6.609614417</td>
<td>5.2 below</td>
</tr>
<tr>
<td>CB3 Sample at leukemia</td>
<td>5.613326152</td>
<td>6.2 below</td>
</tr>
<tr>
<td>CB4 Count recovery post-chemo</td>
<td>6.487553573</td>
<td>5.1 below mean</td>
</tr>
</tbody>
</table>

**Peripheral Blood Telomere Length**

- Healthy subjects
- Cord blood
- Pre-Tx
# CLINICAL PRESENTATION OF HEMATOLOGIC DISEASE IN PATIENTS WITH VERY SHORT TELOMERES

<table>
<thead>
<tr>
<th>Presenting Disease</th>
<th>Total</th>
<th>Unknown Mutation*</th>
<th>TERT</th>
<th>TERC</th>
<th>DKC1</th>
<th>TERF2</th>
<th>TINF2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe aplastic anemia (SAA)</td>
<td>47</td>
<td>28</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis associated SAA</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate AA</td>
<td>34</td>
<td>8</td>
<td>12</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Myelodysplasia</strong></td>
<td>12</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Large granular lymphocytosis</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia + macrocytosis</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Idiopathic neutropenia</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>114</td>
<td>47</td>
<td>46</td>
<td>17</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Townsley D et al, ASH abstract 2012
TELOMERE DISEASE PRESENTING AS MDS

54 y/o man: pancytopenia, dysplastic marrow and abnormal cytogenetics (dup chr 1 and tri 8)

IPSS score = 1; red blood cell transfusion-dependent

RBC tx-dependent

Very short telomeres and novel TERT mutation 1760 T/C (I587T)

Response to Danazol

<table>
<thead>
<tr>
<th></th>
<th>0 Months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>7.6 (tx)</td>
<td>9.2</td>
<td>11.5</td>
</tr>
<tr>
<td>Reticulocytes (k/uL)</td>
<td>16</td>
<td>83</td>
<td>106</td>
</tr>
<tr>
<td>Neutrophils (k/uL)</td>
<td>1.7</td>
<td>3.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Platelets (k/uL)</td>
<td>89</td>
<td>150</td>
<td>120</td>
</tr>
<tr>
<td>Telomere length (kb)</td>
<td>6.2</td>
<td>6.7</td>
<td>6.7</td>
</tr>
</tbody>
</table>
CLINICAL PRESENTATION OF HEMATOLOGIC DISEASE IN PATIENTS WITH VERY SHORT TELOMERES

- PNH clones observed in a minority (14/114) of cases

- Only 45 patients with family histories suggestive of an inherited bone marrow failure syndrome

- Response to immunosuppressive therapy
  - 13/28 (46%) subjects with clinical hematologic response
    (5 later relapsed)
DNA quality (degraded DNA → spuriously long telomeres by pcr)
WBC telomeres = other tissues (testis, for example)?
Normal telomere length in clinically suggestive pedigrees
Leukocyte subpopulations versus total WBC
Median (pcr) versus individual cells/chromosomes (STELA)
Short(er) telomeres due to physiologic (regeneration) and pathophysiologic effects (post-IST, BMT, chemotherapy)
1062 polymorphism vs mutation (genomic architecture?)
Regulatory mutations and polygenic effects
FIRST PATHOLOGIC MUTATION IN HUMAN CCAAT BOX

TERC promoter region: -58C>G (CCAAT>GCAAT)

-58C>G disrupts CCAAT box in TERC promoter region

Aalbers AM et al Blood 2012; 119:3060
STELA IN PHYSIOLOGIC AND PATHOLOGIC TELOMERE ATTRITION PROGRESSION FROM SAA TO MDS
TELOMERE SHORTENING: TISSUE REPAIR AND REGENERATION

Telomere repair mutations:
TERT, TERC, etc.

Telomere erosion

Environment:
immunity, toxins, infections, etc.

stem cell loss
Bone marrow failure

aberrant repair/regeneration
Pulmonary fibrosis Cirrhosis
TELOMERE DISEASES

Disease Risk Factors
- cirrhosis
- pulmonary fibrosis
- immune, virus, toxin
- marrow failure

DKC Complex
- Liver
- Lung
- BM
- Skin/mucosa

Disease Risk Factors
- EtOH
- smoking

Environment

Genetic penetrance
“SHANK’S DISEASE” IN A MENNONITE FAMILY

38 y/o liver transplant

71 y/o thyroid disease

died age 65 yr “blood disease” with pallor

44 y/o androgen-responsive AA/pulmonary fibrosis

47 y/o macrocytosis

died age 33 yr MDS/AML

26 y/o AA

26 y/o dairy farmer
progressive pancytopenia
no response to CSA, hormones

HSCT from sister
minimal GVHD, full recovery

26 y/o
18 y/o
23 y/o
21 y/o macrocytosis

4 y/o

wt hTERT
heterozygous K570N
not tested
dead
**TERT IN ACUTE LEUKEMIA**

Brazil Cohort

N=133 consecutive AML patients (200 matched blood donors; p = 0.0001)

11 TERT mutations: 7 heterozygous, 1 homozygous for A1062T
1 heterozygous H412Y
1 heterozygous R522K
1 heterozygous P65A

TERT- AML: 2 inv(16), 1 complex, t(5;11)(q35;q13) + del(10)(p15), 3 t(15,17)

MD Anderson Cohort

N= 89 selected AML by cytogenetics (528 healthy controls; p=0.028)

4 TERT mutations: 2 heterozygous for A1062T
1 homozygous for 411E deletion
1 heterozygous for V299M

Mutations associated with trisomy 8 and inv(16)

TERT mutations are constitutional and dominant loss-of-function.

Proc Natl Acad Sci USA [II] 2009; 361:2353
TELOMERE SHORTENING IN ACQUIRED APLASTIC ANEMIA

Progressive Telomere Shortening in Aplastic Anemia
By Sarah E. Ball, Frances M. Gibson, Siân Rizzo, Jennifer A. Tooze, Judith C.W. Marsh, and Edward C. Gordon-Smith


Telomere length in leukocyte subpopulations of patients with aplastic anemia
Tim H. Brümmendorf, Jaroslaw P. Maciejewski, Jennifer Mak, Neal S. Young, and Peter M. Lansdorp

BLOOD, 15 FEBRUARY 2001 • VOLUME 97, NUMBER 4

Shortest telomeres in patients with clonal evolution [Ball S et al]
TELOMERE LENGTH AS A PREDICTIVE MARKER IN SEVERE APLASTIC ANEMIA

• N = 183 consecutively treated patients, Clinical Center, 2002-8
• Leukocyte telomere length measured by q-pcr
• Samples obtained pre-IST
• One patient retrospectively identified with TERT mutation

• Telomere length unrelated to primary response to ATG!
• Short telomere length doubles risk of relapse.
• Short telomeres increase risk of clonal evolution 5-6-fold.

TELOMERE LENGTH AND CLONAL EVOLUTION IN SAA

A

EVOLUTION RATE

1.0
0.8
0.6
0.4
0.2
0.0

Follow-up, years

Log rank P=0.009

No. at risk

TL < 1st quartile 46 42 30 26 17 14 9
TL > 1st quartile 137 124 120 94 73 62 42

B

MONOSOMY 7 EVOLUTION

1.0
0.8
0.6
0.4
0.2
0.0

Follow-up, years

Log rank P=0.002

No. at risk

TL < 1st quartile 46 43 33 28 20 16 10
TL > 1st quartile 137 128 124 99 78 66 45
SHORT TELOMERE FREE-ENDS AND TRANSLOCATIONS IN AA COHORTS

Long telomeres

Short telomeres

Calado R' et al
Leukemia 2012; 26:700
TELOMERES, ANEUPLOIDY, AND CANCER

iatrogenic: marrow stress 2° chemotherapy, HSCT

physiologic: aging

constitutional: TERT, TERC, SBDS, DDX11 mutations

telomere erosion

end-end fusion
unbalanced translocations
gain/loss of chromosomal DNA

+mutation/selection

malignant transformation
TELOMERE ATTRITION AND CANCER

Liver
Lung
BM
Skin/mucosa
Hepatic cirrhosis
Aplastic anemia

general cancer risk: AML, GI, lung, GU, others

Immune/inflammatory diseases

AA → MDS and AML
Barrett’s → esophageal cancer
IBD → colon cancer

DKC: cancer of the tongue, AML

Skin/mucosa
Liver
Lung
BM

specificity
penetrance
TARGET PATHOPHYSIOLOGIES FOR ACCELERATED TELOMERE EROSION

peptic reflux / Bardrett’s esophagus / esophageal cancer

chronic hepatitis B virus / cirrhosis / hepatocellular cancer

smoking / cystitis / bladder cancer

gut flora / inflammatory bowel disease / colon cancer

alloantigens / GVHD / late cancers post-transplant

iatrogenic hematopoietic stress post-chemo/radiation therapy
Anabolic Androgenic Steroids in the Treatment of Acquired Aplastic Anemia

By L. Sanchez-Medal, A. Gomez-Leal, Lorenzo Duarte and Maria Guadalupe Rico
SEX HORMONES INCREASE TELOMERASE ACTIVITY IN CULTURED HUMAN LYMPHOCYTES

Calado RT et al, Blood 2009; 114:2236
TELOMERE LENGTH MODULATION BY ANDROGENS
POST-BONE MARROW TRANSPLANT
(LIMITING NUMBERS Terc+/- DONOR CELLS [5X10^5/RECIPIENT])

EXPERIMENT 1

-10
-5
0
5
10
15

0 1 2 3 4

Months after treatment

Kbs

Corn Oil (vehicle; N=3)
Testosterone (350 ug/mouse/week s.c.; N=3)

EXPERIMENT 2

-4
-2
0
2
4

0 1 2 3 4

Months after treatment

Kbs

Corn Oil (vehicle; N=3)
Testosterone (350 ug/mouse/week s.c.; N=3)

Chen J et al, Blood 2012 (ASH abstracts)
TELOMERE LENGTH MODULATION BY ANDROGENS
TBI OF HETEROZYGOUS Terc+/- ANIMALS
(6 GY/ANIMAL/MONTH X 3)

Months after treatment

Kbs

Corn Oil (vehicle; N=2)
Testosterone (350 ug/mouse/week s.c.; N=4)
11-H-0209: “Danazol for Genetic Bone Marrow and Lung Disorders”

Danazol, 800 mg/d x 2 yrs for patients with short telomeres +/- mutations

Phase I/II design, N=25

Primary clinical end points
  toxicity (especially hepatic)
  efficacy (blood counts and pulmonary function)

Protocol opened 19 Aug 2011; 15 patients enrolled to date

Modest drug toxicity (minimal ↑LFTs, mild headaches)

ClinicalTrials.gov identifier: NCT01441037
DOES FAILURE TO RESPOND TO IMMUNOSUPPRESSION REFLECT RESIDUAL STEM CELL NUMBERS?

↑ probability of failure

↑ probability of recovery

(lower limit of accurate in vitro assays)

(stem cell number)

(correlation with blood counts, age)
1. Pre-treatment and post-treatment blood counts predict survival.
2. Children have highest response, recovery, and survival rates.
3. Clonal evolution (MDS, AML, 7-) unusual in CR.
ELTROMBOPAG BIOLOGY

• Small molecule, non-peptide, orally administered thrombopoietin mimetic
• FDA approved for treatment of chronic refractory ITP
ELTROMBOPAG FOR REFRACTORY SAA

Median follow up 13 months (range 4-28 months)

26 patients enrolled

1 patient ineligible, not treated

25 evaluable patients

14 non-responders
- 10 stable disease
- 2 died of progression
- 2 clonal evolution to MDS
  - 1 died
  - 1 HSCT

11 responders (44%)
- 9 platelet responses
- 2 hemoglobin responses
  - additional 4 at > 16wks
- 4 neutrophil responses
  - additional 3 at > 16wks
MULTI-LINEAGE HEMATOLOGIC RESPONSES TO ELTROMBOPAG

Platelets

Neutrophils

Hemoglobin

Trilineage = 6
Bilineage = 7
Unilineage = 4
PLATELET RESPONSES AFTER ELTROMBOPAG

Median platelet increase 39,000/μL (at censure)
HEMOGLOBIN INCREASES AFTER ELTROMBOPAG

Median hemoglobin increase 3.8 g/dL (range 1.5-8.2 g/dL)
BONE MARROW CELLULARITY AT ONE YEAR
IN FOUR RESPONDING PATIENTS
A MECHANISM OF ACTION FOR ELTROMBOPAG IN SAA

immune attack

IST (-)

HSC GROWTH FACTOR (+)

↑ probability of failure

↑ probability of recovery

stem cell number

correlation with blood counts, age, telomere length
MECHANISMS OF ACTION OF TPO VS ELTROMBOPAG

Normal HSCs in niches
- Cellular receptor competition/ internalization/ degradation

TPO
- Plasma protein binding/ degradation

Physiologic

Pharmacologic

eltrombopag
+ Small molecule kinetics

Aneuploid or mutated HSC
HEMATOLOGY BRANCH, NHLBI

Rodrigo Calado
Philip Scheinberg
Sachiko Kajigaya
Jichun Chen
Hiroki Yamaguchi
Thomas Winkler
Mary Morgan
Jake Decker
Cynthia Dunbar
Anna Aalbers
Regis Peffault-Latour
Yasutaka Ueda
Danielle Townsley
Bogdan Dumitrou