Bone Marrow/Hematopoietic Cell Transplantation for Marrow Failure

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Before and during the Transplant

Important issues to consider:
• Do I have the right diagnosis?
• Is transplantation appropriate?
• Do I have a donor?
• What types of stem cells?
• What conditioning regimen?
• Will the donor cells engraft?
• Will I develop GVHD?

Marrow Failure

• Acquired
  – Aplastic anemia
  – Myelodysplasia
  – PNH
  – Marrow Fibrosis
  – Pure Red Cell Aplasia
  – Infiltrating/Metastatic Disease
  – other
• Congenital

BONE MARROW FAILURE SYNDROMES

Normal BM

Aplastic Anemia
MDS
(RARS-T with multilineage dysplasia)

Treatment options are dependent upon the correct diagnosis

Considerations before transplantation

- Severity of the Disease
  - Disease Duration
  - Prognosis
- Do we understand the mechanism(s) of the disease?
- Treatment Options
  - Side effects/Mortality
  - Donor Availability
- Patient Age
- Comorbid Conditions
- Health Care Cost

IST for AA – Survival Rates Over Time
Impact of improved supportive care


Eltrombopag

- Small molecule, non-peptide, orally administered thrombopoietin mimetic
- Not FDA approved for AA

MDS
5-Azacitidine and Overall Survival in MDS & AML

Proportion Surviving

Time (months) From Randomization

113 AML
245 MDS

P=0.0001
HR=0.58 (95% CI: 0.43-0.77)


PNH

Actuarial Survival from the Time of Diagnosis in 80 Patients with PNH

 Patients Surviving (%)

Years after Diagnosis

Eculizumab ↑
Agra and cell matched control


Donors?

- **HLA matched**
  - Full siblings
  - Unrelated volunteers (NMDP etc)

- **HLA mismatched**
  - HLA haploidentical family members
  - Unrelated volunteers

- **Umbilical Cord blood (unrelated or related)**

The Family Study

Parents

Children

50% 25% 25%
Major Parts of Transplantation

• Conditioning
• Donor cell infusion
• GVHD prevention
• Other
  – Prevention of
    • Rejection
    • Infection
  – Treatment of
    • Rejection
    • Relapse

Why and How to Condition

• Purpose
  – Suppress the immune system
  – Kill disease cells
• Options
  – Irradiation
  – Chemotherapy
  – Immunosuppressive drugs
  – “targeted” therapy
• Potential problems
  – “Systemic” effects and toxicity
• Important
  – Coordinate conditioning with other therapy given before transplantation

Types/sources of stem cells

Infused i.v.

• Bone marrow
• Blood after “mobilization” with growth factor (G-CSF)
• Cord blood cells

Aplastic Anemia (AA)

AA Conditioning Regimens

• Cyclophosphamide (CY)
• CY + Anti-thymocyte globulin (ATG)
• CY + ATG + Total body irradiation (TBI)
• Fludarabine (Flu) + ATG + TBI
• Flu + CY + ATG + TBI
• CY + Flu + TBI
• etc

AA - Survival after URD Marrow Transplantation

P. Anderlini et al, Lancet Haematology, 2015
MDS Conditioning Regimens
(High intensity and reduced intensity)

- Flu + Busulfan (BU)
- BU + CY
- Flu + Melphalan (Mel)
- Flu + Mel + TBI
- Flu + Treosulfan (Treo)
- Flu + Treo + TBI
- Flu + Thiotepa + TBI
- etc

Total Body Irradiation
Radioimmunotherapy

Transplants for MDS - Survival

RIC in patients 60 – 70 ys of age
(by IPSS risk)

PNH Conditioning

- Dependent upon presentation
  - Like AA
  - Like MDS/leukemia

HCT for PNH (EBMT)
Questions?

And after Transplantation?

Engraftment
• Definition:
  – Donor cells have established themselves and begin to produce new cells in the patient
• How do you know?
  – Rise in neutrophil (poly) count
  – Rise in platelets
  – Rise in red blood cells (later)

Graft Failure
• Donor cells fail to engraft in the marrow and do not produce new cells
  – Primary – neutrophils never rise appropriately
  – Secondary - Donor cells initially establish themselves, but after initial recovery, the counts decline and the graft may be lost

Acute Complications
• “Toxicity”
  – Mouth (mucositis)
  – Gut (Nausea, vomiting, diarrhea)
  – Lungs (pneumonia)
  – Liver (jaundice)
• Infections
• Acute GVHD
• Bleeding

GVHD
• Donor stem cells produce immune cells. They recognize the new environment (the patient) and “get turned on”.
• These turned-on donor cells can attack and damage the patient’s body → GVHD
• GVHD can be acute, chronic (or both)
GVHD Prophylaxis

- Preventing the undesired effect of donor immune cells (T cells) by
  - Removing (naïve) T cells from donor cells before infusion
  - Eliminating donor T cells/T cell effects after donor cell infusion by treating the patient
    - CSP, Tacrolimus, MTX, Sirolimus, cyclophosphamide
- Changing the patient’s internal environment
  - Bacteria in the gut

Intestinal Bacteria and GVHD

Delayed complications

- Chronic GVHD
- Infections
- Hormone deficiencies (menopause, infertility, growth and development, thyroid)
- Ocular complications
- Muscle and bone damage (osteoarthritis, avascular necrosis)
- Psycho-social
- New cancers
- Relapse of primary disease
Increased Rate of Chronic GVHD

Related to …

- Decreased acute early transplant-related mortality
- Older patients
- Peripheral blood as source of stem cells
- Expansion of donor pool (unrelated, mismatched)
- Use of donor lymphocyte infusion (DLI)

Sites Affected by Chronic GVHD

Randomized comparison of BM and PBPC

Flowers et al, Blood 2002;100: 415-419

Better GVHD Prevention

- ATG (thymoglobulin)
- Cytoxan after donor cell infusion
- Triple combination:
  - Cyclosporin (or tacrolimus) + MMF + sirolimus
- New agents
  - Ruxolitinib (Jakafi)
  - Proteasome inhibitors
  - Alpha 1 anti-trypsin
  - other

Chronic GVHD

Immune Dysfunction

- Immune dysfunction is hallmark of the disease
- Low numbers of T and B cells, inverted CD4:CD8 ratio
- Low IgG (or subclasses)
- Susceptibility to opportunistic infections
- Treatment with immunosuppressive agents further compromises immune dysfunction

Aplastic Anemia, Long-term Results

G.Georges et al
Breast Cancer by TBI Conditioning
(Female 5-year Survivors)

<table>
<thead>
<tr>
<th>Years after HSCT</th>
<th>Probability of Secondary Breast Cancer</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0.17</td>
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<tr>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>15</td>
<td>0.15</td>
</tr>
<tr>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

(p < 0.001, Gray's test)

Bone complications

Avascular necrosis
- 5-22%
- Hip joints; multiple joints
- Surgical replacement
- Core decompression (release pressure)

Bone loss
- >15% by one year after transplant
- 10% fractures in patients surviving >1 yr

Major impact in quality of life (QOL) due to pain and limited mobility

Mental issues among adult HCT survivors

> Sustained attention, screening out distractions
> Speed of information processing
> Memory: acquisition and retrieval
> Executive function
  - Planning and organizing
  - Complex attention
  [Multi-tasking]

Sexual Function (N=161)

<table>
<thead>
<tr>
<th>Years after Transplant</th>
<th>Sexual Function Mean Score ± se</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo. - 2 yrs</td>
<td>Male Controls: P = .02</td>
</tr>
<tr>
<td>6 mo. - 5 yrs</td>
<td>Male Survivors: P = .01</td>
</tr>
<tr>
<td>6 mo. - 5 yrs</td>
<td>Female Controls: P = .03</td>
</tr>
<tr>
<td>6 mo. - 5 yrs</td>
<td>Female Survivors: P = .17</td>
</tr>
</tbody>
</table>

40% Females Inactive At All Times


Probability of Survival for Patients who are alive 2 yrs after transplantation

<table>
<thead>
<tr>
<th>YEARS</th>
<th>PROBABILITY OF SURVIVAL</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
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<tr>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
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<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
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</table>

Patient-reported Quality of Life

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>Mean</th>
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</thead>
<tbody>
<tr>
<td>Physical Health</td>
<td>2-4</td>
<td>10</td>
<td>8-9</td>
<td>8.8-8.6</td>
</tr>
<tr>
<td>Psychological Health</td>
<td>1-3</td>
<td>10</td>
<td>8.5-9</td>
<td>8.1-8.5</td>
</tr>
<tr>
<td>Social Interactions</td>
<td>1-3</td>
<td>10</td>
<td>9-10</td>
<td>8.4-8.9</td>
</tr>
<tr>
<td>Memory &amp; Concentration</td>
<td>1-3</td>
<td>10</td>
<td>8-9</td>
<td>7.6-8.1</td>
</tr>
<tr>
<td>Severity of Symptoms</td>
<td>1</td>
<td>8-10</td>
<td>1-2.2</td>
<td>2.7-3.4</td>
</tr>
</tbody>
</table>

* Given are the ranges at 2-20 years
Summary

- Transplantation is effective therapy for AA, MDS, PNH
- Success rates have progressively improved
- However, there are potential problems
  - Toxic effects of conditioning - usually manageable
  - Graft failure – not frequent
  - GVHD – maybe 30% - 40%
  - Late effects

Success of HCT depends on:

- Type of disease
- Disease stage
- Patient age and overall condition
- Donor age ???
- The development of (chronic) GVHD
- Other delayed complications

Survival in post-AA MDS

Success of HCT depends on:

- Type of disease
- Disease stage
- Patient age and overall condition
- Donor age ???
- The development of (chronic) GVHD
- Other delayed complications

Fasciitis and scleroderma

Survival in post-AA MDS

Survival in post-AA MDS

Cytogenetics and Outcome in Flu/Treo/TBI conditioned MDS patients (n=36)
Transplantation for PNH at FHCRC

• Indications
  – Aplastic phase n=12
  – Hemolysis, thrombosis n=16
  – Preogression to MDS/AML

Transplantation for PNH (IBMTR)

• PNH 39
• PNH to AA 16
• AA to PNH 2

Total 57


Transplantation for PNH (IBMTR)

• Conditioning Regimens
  – BUCY
  – CY TBI
  – CY LFI
  – CY
  – None

Transplantation for PNH (IBMTR)

Survival by Donor Type

• Donor Type
  – HLA-ID sib 48
  – Syngeneic 2
  – URD 6
  – Haploidentical 1

• Survival
  – 27 (at 2 yr)
  – 2 (8 and 12 yr)
  – 1 (5 yr)
  – 0

Immunosuppressive Therapy

• Horse ATG +/- other agents
• Rabbit ATG
• Campath (Alemtuzumab)
• Eltrombopag
• Other

Bone marrow failure syndromes—Bone marrow is unable to keep up with the body’s need for healthy blood cells

Acquired
  – Idiopathic
  – Myelodysplastic syndromes (MDS)
  – Toxins (e.g., drugs, irradiation, infections)

Inherited* - Diamond-Blackfan anemia
  – Fanconi anemia
  – Shwachman-Diamond
  – Telomere biology disorders
  – Others

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Inherited* - Diamond-Blackfan anemia
  – Fanconi anemia
  – Shwachman-Diamond
  – Telomere biology disorders
  – Others
ATG AND CSA FOR SEVERE APLASTIC ANEMIA

**BLOOD COUNTS at 3 MONTHS and SURVIVAL**

Survival Probability in Children

**Overall**

**Responders to IST**

Randomized Trial of H-ATG vs. R-ATG in SAA - Survival

Follow-up, all patients = median 839 (range, 2–1852) days
Follow-up, surviving patients = median 891 (range, 185–1852) days

Ph. Scheinberg et al, NHLBI

IST FOR APLASTIC ANEMIA

Limits to Efficacy

- **Unresponsiveness**
  - Severe stem cell deficit (Quantitative?) (Telomeres?)
  - Autoreactive cells not responsive to immunosuppressants (MMF, Rapa, Alemtuzumab)

- **Relapse**
  - Continuing “subclinical” immune destruction of stem cells
  - Hematopoietic exhaustion

- **Evolution**
  - Pre-existent clones?
  - Genomic instability (Telomeres?)

Refractory to equine ATG (Atgam)

- Rabbit ATG
- Alemtuzumab
- Eltrombopag
- Transplantation
**SAA refractory to equine ATG – salvage with rabbit ATG + CsA**

2/3 Response rate -
But other data: ~30%-40% responses

Scheinberg P, Nunez O, Young NS. Br J Haematol 2006

**CYTOGENETIC EVOLUTION with IST (N=189)**

Ph. Scheinberg et al, NHLBI

**SAA Eltrombopag Study Results**

Censure date 11/1/2011

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

26 patients enrolled

1 patient ineligible, not treated

11 responders (44%)
• 9 platelet responses
• 2 hemoglobin responses
• additional 4 at > 16wks
• 4 neutrophil responses
• additional 3 at > 16wks

25 evaluable patients

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


**MULTI-LINEAGE HEMATOLOGIC RESPONSES TO ELTROMBOPAG**

P. Scheinberg et al, NHLBI

Telomere Diseases
**TELOMERE STRUCTURE**


**TELOMERE LENGTH IN TERT MUTATED LEUCOCYTES**

H. Yamaguchi et al, NEJM, 2005

**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

**TELOMERE SHORTENING: TISSUE REPAIR AND REGENERATION**

Telomere repair mutations:  
- TERT, TERC, etc.  
- telomere erosion

Environment:  
- immunity, toxins, infections, etc.

- stem cell loss  
- aberrant repair/regeneration  
- Bone marrow failure  
- Pulmonary fibrosis  
- Cirrhosis

**TELOMERE LENGTH AS A PREDICTIVE MARKER IN SEVERE APLASTIC ANEMIA**

- 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


**TELOMASE MUTATIONS AND PULMONARY FIBROSIS**

Transplantation for AA

Aplastic Anemia: Survival after CY + ATG conditioning and HLA-identical sibling transplantation

Storb et al, BBMT

HCT for AA after conditioning with CY + Flu + Campath

Related and unrelated donors


Immunosuppression or BMT?

Aplastic Anemia


Donor Chimerism

CD15
CD3
UF


Probability

Years

Aplastic Anemia: Survival after CY + ATG conditioning and HLA-identical sibling transplantation

Storb et al, BBMT

HCT for AA after conditioning with CY + Flu + Campath

Related and unrelated donors


Immunosuppression or BMT?

Aplastic Anemia


Donor Chimerism

CD15
CD3
UF

HLA = siblings, > 40 years

Sib BMT <20 yy CY200+ATG+ BM
Sib BMT >40 yy Flu CY ATG +BM
Sib BMT 20-30 early CY200+ATG+ BM
Sib BMT 20-30 LATE Flu CY ATG +BM
Sib BMT 30-40 Flu CY ATG +BM
URD BMT <14 Flu CY ATG/C +BM
URD BMT >14 Flu CY ATG/C +TBI 200 +BM

Current BMT CTN Trial for URD for A (0301)

- Objectives:
  Further reduce regimen-related toxicity and GVHD

- Strategy:
  - ATG + 200 cGy TBI + Flu x 30 + "optimization" of CY (250 vs 100 vs 50 vs 0)

Study closed. Final decision between CY 50 and 100
### 5-Group Cytogenetic Classification

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Cytogenetic Abnormality</th>
<th>Survival (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very good</strong></td>
<td>del(11q)</td>
<td>60.8 (50.3–NR)</td>
</tr>
<tr>
<td><strong>Good</strong></td>
<td>del(5q) del(7q) incl.del(5q)</td>
<td>46.6 (44.4–54.3)</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>del(7q), i(17q), +19, any other</td>
<td>26.0 (22.0–31.0)</td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td>del(3)(q21;q26), -7 incl. -7, del(7q) 3 abnl.</td>
<td>15.8 (12.0–18.0)</td>
</tr>
<tr>
<td><strong>Very poor</strong></td>
<td>≥4 abnl.</td>
<td>5.9 (4.8–6.9)</td>
</tr>
</tbody>
</table>

*J. Schanz et al, JCO, 2011*

### IPSS-R Prognostic Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>0</th>
<th>0.5</th>
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<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Cytogenetics*</td>
<td>Very Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marrow Blasts (%)</td>
<td>≤2</td>
<td>&gt;2 ≤5</td>
<td>5–10</td>
<td>&gt;10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8–&lt;10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50–100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Neutrophils</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
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</table>

### IPSS-R Scores and Expected Survival (Years)

<table>
<thead>
<tr>
<th>Patient Age (ys)</th>
<th>Very Low (0–1.5)</th>
<th>Low (1.5–3)</th>
<th>Intermediate (3–4.5)</th>
<th>High (4.5–6)</th>
<th>Very High (&gt;6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤60</td>
<td>8.8</td>
<td>5.2</td>
<td>4.5</td>
<td>4.6</td>
<td>4.8</td>
</tr>
<tr>
<td>&gt;60</td>
<td>NR</td>
<td>8.8</td>
<td>5.2</td>
<td>4.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*P. Greenberg et al, Blood 2012*

### Lenalidomide

**Duration of Major Erythroid Responses (Deletion 5q; n=114)**

- Median duration Txi ≥2.2 years
- Median F/U: 2.8 yr (Max 4.4 yr)
- Min, max = 0.2, 4.4+ years

*Censored patients who remain Txi at time of data cut-off (Dec. 2006) or at time of study discontinuation.

### 5-Azacitidine and Overall Survival in MDS & AML

- **P=0.0001**
- HR=0.58 (95% CI: 0.43–0.77)
- **Median OS (months):**
  - 113 AML: 245 MDS: 24.5 months
- **Survival by salvage treatment in azacitidine treated patients**
  - Th. Prébet et al. JCO 2011;29:3322-3327
  - HCT
Induction chemotherapy or hypomethylating agents before HCT?

Ongoing Study

Post-transplant relapse and survival after IC or hypomethylating therapy

Transplantation

Relapse by 5-Group Karyotype

Monosomal Karyotype, Relapse and Survival
Conditioning Regimens and Survival

![Graph showing survival probabilities after transplant](image)

The molecular landscape

Mutations in candidate genes and survival (no transplants)

Candidate Genes
- TET2
- ASXL1
- RUNX1
- TP53
- EZH2
- NRAS
- JAK2
- ETN6
- CBL
- B2H2
- NPM1
- IDH1
- KAS6
- GNAS
- PTPN11
- BRAF
- PTEN
- CDKN2A

Functional impact?

SF3B1 Mutation and Prognosis

- Overall Survival
- Leukemia-free Survival
Gene expression signature and survival

Let-7b is inversely correlated with EZH2

Let-7b and EZH2 expression

Treosulphan Conditioning

Conditioning Regimens and Survival

Flu/Treo Conditioning
Flu + Treo Conditioning: Impact of Karyotype

E. Nemecek et al., BBMT, 2011

Flu/Treo/TBI Treatment Scheme

Gyurkocza et al., BBMT, in press

Impact of Cytogenetics in MDS (n=36)

Gyurkocza et al., BBMT, in press

**Comorbidities and survival without transplantation**

- Comorbidities (ACE-27) had no significant impact on survival
  - in patients ≤65 years
  - in patients with low risk MDS
- Age ≥ 65 years - poorer survival
- Age ≥ 65 years - greater co-morbidities
- Greater co-morbidities → poor candidates for HCT

K. Naqvi et al. JCO 2011
Risk model for non-transplanted patients:

- \( \uparrow \) IPSS
- Age \( \geq 65 \)
- \( \uparrow \) Comorbidity

Current CTN Trial 0901

- MDS/AML
- \(< 5\% \) blasts
- Age 18-65 yrs

Enrollment / Randomization

RIC Regimens
- Flu/Bu
- Flu/Mel

High Intensity Regimens
- Bu/Flu
- Bu/Cy
- Cy/TBI

Primary Endpoint: 18-months Overall Survival

Other non-HCT Therapy

- Epo + G-CSF
- TPO receptor agonists
- Immunosuppression
- TLK 199
- Combinations

- Decitabine
- HDAC
- Proteasome inhibitors
- Clofarabine
- ON 01910
- Combinations

Target the “SOIL” in addition to the seed

A. Verma, H.J. Dong et al
Summary and Conclusions

• Therapy for AA is well “established”, however, there are still questions regarding older patients and URD transplant.
• The development of optimal treatment strategies for MDS is still in flux, in particular for patients with “low risk” disease and older individuals.
• New genomic/molecular insights are expected to change approaches to both MDS and AA.

Thank you

• Phil Scheinberg
• Rodrigo Coldado
• Andrea Bacigalupo

TELOMERE ELONGATES THE 3' END OF TELOMERES BY ADDING TTAGGG REPEATS

TELOMERE DISEASES

Disease Risk Factors

DKC Complex

Disease Risk Factors

Liver

Lung

BM

Genetic Penetrance

Physiologic Aging

Skin / Mucosa

Hepatic Cirrhosis

Pulmonary Fibrosis

Aplastic Anemia

Marrow Failure

Environment

Immune, Viral, Toxin

EtOH

Smoking

Sib BMT < 20 yy

Sib BMT > 40 yy

CY200 + ATG + BM

Flu CY ATG + BM
**PNH**

- Defect in GPI-anchored proteins (PIG-A mutation) associated with:
  - Hemolysis
  - Vascular complications
  - Peripheral blood cytopenias
  - Development of AA or Transformation to MDS/AML

Incidence of MDS by Age

5-AZA responses are slow....

Cumulative Probability

<table>
<thead>
<tr>
<th>Time (cycles)</th>
<th>Number of Patients</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
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<tr>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
</tr>
</tbody>
</table>

87%, 6 cycles

50%, 2 cycles

Range: 1-22 cycles


Risk factors with 5-azacitidine treatment

<table>
<thead>
<tr>
<th>Poor Response</th>
<th>Reduced Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior low-dose Ara-C</td>
<td>Performance status ≥ 2</td>
</tr>
<tr>
<td>Marrow blasts &gt; 15%</td>
<td>Intermediate/poor risk cytogenetics</td>
</tr>
<tr>
<td>Abnormal cytogenetics</td>
<td>Circulating blasts</td>
</tr>
<tr>
<td>Better response</td>
<td>TET2 mutation? ≥ 4 units pRBC / 8 weeks</td>
</tr>
</tbody>
</table>

Ilykson et al, Blood 2010

CURE

H.J. Deeg

Link between karyotype and non-relapse mortality:

Impact of HCT-CI and GVHD?

HCT-CI and acute GVHD grades III-IV

M.Gomer et al, unpub.

Clonal architecture in MDS

**Outcomes by Diagnosis**

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML (n=60) – 32%</td>
<td>68%</td>
</tr>
<tr>
<td>MDS (n=36) – 20%</td>
<td>74%</td>
</tr>
</tbody>
</table>

p = 0.20

Gyorkocza et al, BBMT, in press

**AML – Impact of MRD**

(n=56, in morphologic remission)

Gyorkocza et al, BBMT, in press

**HCT for Advanced MDS, Age >50 ys (1998–2006)**

And survival after 5-aza

Median survival in 5-aza responders

CIBMTR

R. Wells

**Randomized Trial of H-ATG vs. R-ATG in SAA - Survival**

Horse ATG vs. Rabbit ATG

P = 0.392

Ph. Scheinberg et al, NHLBI

**Characteristics of β-, α- emitters**

Normal tissue

J. Pagel
FAB Classification: Pathology Slides

RAEB

RAEB: Note agranular myelocytes and agranular poorly segmented neutrophil, and abnormal basophil with dense nuclear chromatin (arrowed)

RAEB-T

RAEB-T: Two myeloblasts, one with an Auer rod, and a quadranucleate normoblast

Images Courtesy of HMDS, Leeds, UK

SAA - Overall survival after URD Marrow Transplantation

CY DL 0 at 1 year: 50.0 % (95% CI: 0.6 %, 91.0 %)

CY DL 50 at 1 year: 96.8 % (95% CI: 79.2 %, 99.5 %)

CY DL 100 at 1 year: 74.1 % (95% CI: 53.2 %, 86.7 %)

CY DL 150 at 1 year: 60.0 % (95% CI: 25.3 %, 82.7 %)

P. Anderlini et al, under review