Conditioning Regimens and Stem Cell Sources for Allogeneic Hematopoietic Cell Transplantation in MDS

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DISCLOSURE

I have the following financial relationships:

Consultant for: Medac Pharma, Inc.
Contracted Research for: Celgene Corporation
Transplantation comes as a package:

- Assessment of patient and disease characteristics
- Non-transplant/Pre-transplant therapy
- Stem cell source/Donor selection
- Transplant (HCT) conditioning
- Post-transplant care
  - GVHD prophylaxis
  - Relapse prevention
Background
30 years ago………………..

• 10 patients, transplants from HLA matched siblings
  – 3 conditioned with CY (considered to have aplastic anemia) – persistent/recurrent disease
  – 7 conditioned with CY + TBI – 6 surviving in remission

• **6 of 10 (60%) surviving**

F. Appelbaum et al, Ann Int Med 1984
Relapse-free Survival (N=102)
Patients 6-66 years old, related or unrelated donors

Deeg et al., Blood 2002

Oral tBUCY

IPSS low (N=16)
IPSS int-1 (N=54)
IPSS int-2 (N=24)
IPSS high (N=8)
Relapse

Deeg et al., Blood 2002

Oral tBUCY Related & URD
Conditioning with **BU/CY/TBI** for HCT in MDS

N=25; ages 16-54 (median 41) yrs
30 related = or ≠ 6 URD

J E Anderson et al., *JCO* 14: 220, 1996
Recent Developments
## 5-Group Cytogenetic Classification

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Cytogenetic Abnormality</th>
<th>Survival (ms) Median (CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Single</td>
<td>Double</td>
</tr>
<tr>
<td>Very good</td>
<td>del(11q)</td>
<td>---</td>
</tr>
<tr>
<td>Good</td>
<td>normal</td>
<td>del(5q)</td>
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<td></td>
<td>del(12p)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>del(20q)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q), +8, i(17q), +19, any other</td>
<td>any other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>der(3)(q21;q26), incl. -7, del(7q)</td>
<td>3 abnl.</td>
</tr>
<tr>
<td>Very poor</td>
<td>---</td>
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</tr>
</tbody>
</table>
Relapse by 5-Group Karyotype

- **Very good (n=13)**
- **Very poor (n=109)**
- **Poor (n=159)**
- **Intermediate (n=184)**
- **Good (n=461)**

HJ Deeg et al, Blood, 2012
Survival and relapse by IPSS-R risk.

C

Overall survival

Cumulative Proportion Surviving

IPSS–R risk
Low risk
Intermediate risk
High risk
Very high risk

Time (months)

0 24 48 72 96 120 144

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Is Pre-HCT “pre-conditioning” effective in reducing post-HCT relapse?
Bu Dose Intensity in AML/MDS: Importance of *Disease Status*

BuCy = 12.8 mg/kg iv Bu + 120 mg/kg Cy
FB4 = 150-160 mg/m² Flu + 12.8 mg/kg Bu
FB2 = 150-160 mg/m² Flu + 6.4 mg/kg Bu

Shimoni et al. *Leukemia* 2006;20:322-328
Outcome according to pre-HCT treatment (N=163)

**Survival**

- Overall Survival (probability)
  - AZA alone: HR = 1
  - ICT alone vs AZA alone: HR = 1.41 (95% CI, 0.83 to 2.42); P = ns
  - ICT-AZA vs AZA alone: HR = 3.08 (95% CI, 1.38 to 6.85); P = .006

- No. at risk:
  - AZA alone: 48 43 40 37 35 31 23 15 11 9 7 0
  - ICT alone: 98 87 77 72 65 58 41 51 42 35 30 0
  - ICT-AZA: 17 14 10 7 6 5 5 2 2 0

**RFS**

- Event-Free Survival (probability)
  - AZA alone: HR = 1
  - ICT alone vs AZA alone: HR = 1.48 (95% CI, 0.90 to 2.44); P = ns
  - ICT-AZA vs AZA alone: HR = 2.72 (95% CI, 1.38 to 5.34); P = .01

- No. at risk:
  - AZA alone: 48 43 37 31 28 22 15 11 9 7 0
  - ICT alone: 98 76 65 58 65 54 49 45 44 29 25 0
  - ICT-AZA: 17 13 9 6 6 5 5 2 2 0

**Relapse**

- 3-Year Relapse (probability)

- No. at risk:
  - AZA alone: 48 43 37 33 31 28 22 15 11 9 7 0
  - ICT alone: 98 87 77 72 65 58 41 51 42 35 30 0
  - ICT-AZA: 17 14 10 7 6 5 5 2 2 0

**NRM**

- 3-Year NRM Survival (probability)

- No. at risk:
  - AZA alone: 48 43 37 33 31 28 22 15 11 9 7 0
  - ICT alone: 98 87 77 72 65 58 41 51 42 35 30 0
  - ICT-AZA: 17 14 10 7 6 5 5 2 2 0

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Damaj G et al. JCO 2012;30:4533-4540
Study Schema (FHCRC # 2661)

Potential Patient Identified

Determination of Eligibility

Yes

Obtain Patient Consent and/or Assent

Randomize

Arm A: HMA-based therapy

HCT

No HCT

Arm B: Induction Chemotherapy

Initial Therapy

Follow-up

Assess for Alternative Protocol

No
Which Conditioning Regimen?
Relapse and Non-Relapse Mortality

- Untreated
  - REL=26%
  - NRM=38%

- Treated
  - REL=37%
  - NRM=34%

- Treated, no CR1
  - REL=37%
  - NRM=25%

- Treated CR1
  - REL=27%
  - NRM=25%

Pre-Transplant

CTN Trial 0901 (now closed)

MDS/AML
< 5% blasts
Age 18-65 ys

Enrollment / Randomization

RIC Regimens
Flu/Bu
Flu/Mel

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

Primary Endpoint: 18-months Overall Survival
Age and Co-Morbidities
Survival by Age after NMA Conditioning and HCT for Advanced Hematologic Malignancies

Impact of HCT-CI and the comorbidity/age index (HCT-CI/age)

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Sorror M L et al. JCO 2014;32:3249-3256
Other Conditioning Strategies
Radio-Immuno Therapy

~10 days

0.5 mg/kg $^{131}$I-α-CD45 Ab (4-10 mCi)

0.5 mg/kg $^{131}$I-α-CD45 Ab (escalating Gy to liver)

Flu
30 mg/m$^2$/d

TBI
2 Gy

PBSC

CSP

MMF

J. Pagel

Imaging
OS and PFS – Age < 50 ys, Advanced AML
Flu/Treo Conditioning

- **FLU** 30 mg/m\(^2\)/day
- **TREO** 14 g/m\(^2\)/day
- **HCT**
- **Methotrexate** 10 mg/m\(^2\)/dose
- **Tacrolimus** BID

E. Nemecek et al, BBMT, 2011
Flu + Treo Conditioning: Impact of Karyotype

E.Nemecek et al, BBMT, 2011
**Flu/Treo/TBI Conditioning**

- **TREO 14 g/m²/day**
- **FLU 30 mg/m²/day**
- **TBI 2 Gy**
- **HCT**

Timeline:
- **Days -6 to 0**
- **+1 to +3**
- **+6**
- **+11 to +56**
- **+180**

- **Methotrexate 10 mg/m²/dose**

- **Tacrolimus BID**

Reference:
B.Gyurkocza et al, BBMT, 2014
Impact of Cytogenetics in Flu/Treo/TBI conditioned MDS patients (n=36)

Relapse

Good/Interm (n=20) – 27%

Poor (n=16) – 13%

Survival

Good/Interm (n=20) – 82%

Poor (n=16) – 68%

Months from HCT

B.Gyurkocza et al, BBMT, 2014
Mutations, Conditioning and Gene expression
Conditioning Intensity and minimal residual disease
AML/high risk MDS

![Graph showing percent relapse over years from transplant for different groups: NMA MRD+, MA MRD+, NMA no MRD, and MA no MRD. Graph is sourced from R. Walter et al.](image-url)
Source of stem cells
Survival by donor type

- Matched sib (n=470)
- URD 10/10 (n=266)

Deeg et al, Blood 2012
Relapse-free survival
(694 adult MDS patients)

HLA haploidentical related donors

K. Raj et al, BBMT 20: 890, 2014
Cord blood vs HLA-haploidentical donors

C.G. Brunstein et al, Blood 2011
Summary and Conclusions

• Conditioning strategies continue to evolve
  – Optimum regimen yet to be determined
• Relapse is still an issue in high risk patients
• Donors are available for most patients
• Comorbidities impact outcome
• Results with all stem cell sources have improved in recent years
• GVHD (not discussed) may occur with any stem cell source
Summary and Conclusions

• Pre-transplant “debulking” may select for sensitive vs resistant disease
• Earlier HCT should improve results – less relapse and less NRM
• A place for pre-emptive targeted post-HCT therapy?
Thank you!