Transplantation for MDS in Older Patients

H. Joachim Deeg MD
Fred Hutchinson Cancer Research Center
& University of Washington/SCCA
Seattle, WA

Berlin, September 2011
Yes or No?

• Transplantation is the only modality with proven curative potential,

BUT

• ........should cure always be the goal of therapy?
What therapy are MDS patients receiving?

- ESAs
- G-CSF
- Azacitidine
- Decitabine
- Lenalidomide
- Thalidomide
- Stem Cell Transplant
- Iron chelation
- Immunosuppression
- Clinical trial
- HCT

MDS Foundation Patient Survey (n=359; January-October 2006)

BMF Consortium National MD Survey (n=4,154; June 2005-January 2007)

AA&MDS Int'l Foundation Patient Survey (n=358; March 2009)


Sekeres MA et al *JNCI* 2008; 100:1542-1551
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:

↑ IPSS
Age ≥ 65
↑ Comorbidity

K. Naqvi et al. JCO 2011
Survival After Allo-HCT for Advanced MDS, Age >50 ys, 1998–2006

- Reduced-intensity conditioning, HLA-identical sibling (N=232)
- Myeloablative, HLA-identical sibling (N=318)

(P=0.0004)
...in Comparison to 5-azacitidine

Median survival with 5-aza

Reduced-intensity conditioning, HLA-identical sibling (N=232)

Myeloablative, HLA-identical sibling (N=318)

Probability of Survival

Years
Outcome after Low Intensity Conditioning

Laport et al, BBMT, 2008
Seattle Consortium

120 patients, 42-73 (median 59) years old
All MDS categories
Conditioning with Flu + 2Gy

RFS: HR for >60 years 0.73, p= 0.1
3-year relapse-free survival in patients > 50 years:

95% not cured!

4% – 5%

Age >50y

High intensity

N=171

REL=38%

NRM=57%

Reduced intensity

N=156

REL=59%

NRM=37%

Selection bias

• These results in “older” patients were achieved in individuals deemed suitable for HCT, based on “biologic age”, not on chronologic age.
• Question, therefore: “who is old?”
Survival by salvage treatment in azacitidine treated patients

Th. Prébet et al. JCO 2011;29:3322-3327

<table>
<thead>
<tr>
<th>Type of salvage</th>
<th>N</th>
<th>ORR</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>165</td>
<td>NA</td>
<td>3.6</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>122</td>
<td>NA</td>
<td>4.1</td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>32</td>
<td>0/18</td>
<td>7.3</td>
</tr>
<tr>
<td>Intensive chemotherapy</td>
<td>35</td>
<td>3/22</td>
<td>8.9*</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>44</td>
<td>4/36</td>
<td>13.2*†</td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>37</td>
<td>13/19</td>
<td>19.5*†</td>
</tr>
</tbody>
</table>

HCT
Disease stage, QOL and transplant benefit

• For patients, aged 60-70 years, with *de novo* MDS IPSS low/intermediate-1, early RIC transplantation does not consistently provide life expectancy benefit.

• For patients with IPSS intermediate-2/high, early RIC transplantation offers life expectancy benefit *only with follow-up beyond 5 years*. 

J.Koreth et al, unpublished
Cure is great – but survival is cool, too
….. and when things don’t go well they may go really badly…
HCT should be judged just as other therapies

“Demonstrate efficacy and acceptable safety in adequate and well-controlled studies.”
...or maybe more strictly:

• With our current approach we know that while we often succeed in curing one disease, there is a 50% or higher risk of inducing “secondary” disease, GVHD.

• In other words, patients may have RFS, but not truly DFS!
Chronic GVHD and QOL

Months

A couple of years
WILL I LIVE, DOCTOR?

YES, BUT I DON'T ADVISE IT!!!
Chronic GVHD and consequences

• Older age is associated with increased incidence of chronic GVHD
  – Increased use of steroids
  – Increased NRM related to chronic GVHD
    – HR 1.33, CI 1.2-1.5, p< 0.01

• Older patients tolerate steroids poorly

Vigorito et al Blood, 2009
Other considerations

• Secondary disease can entail devastating complications
• Major demands on the healthcare system
Financial fitness

- Healthcare resources are limited, as is most patients' personal financial reserve
- Lifetime ceiling of insurance coverage
- Major out-of-pocket expenses
- Family may make an enormous investment for a futile effort
Thank you

- Mary Flowers
- Richard Wells
- Ted Gooley
- John Koreth
Who is massively harmed by BMT?

• Patients who:
  – Die within 2 years
  – Relapse soon after BMT
  – Survive, but suffer adverse effects resulting in severely diminished QoL
Other Considerations

• Menschen, ... denen weder Halsentzündung noch Herzversagen etwas anhaben konnten, die aber sich selbst und die Gesellschaft erheblich finanziell belasten, indem sie bis 90 leben, und womöglich noch etwas länger (Steinunn Sigurdardottir)
5-Azacitidine + Etanercept

B. Scott et al, BJH, 148: 944, 2010

Responses by IWG criteria.

B. Scott et al, BJH, 148: 944, 2010
Responses by IWG criteria.
Donor vs. no donor comparison

#1

No donor

Donor

Median age 48
59% >50

Median age 43
77% >50

38/61 patients had ASCT
(1 patient had allo-HCT)

29/39 patients had allo-HCT

N=184; 100 achieved CR

De Witte, Blood (2001)
How to Treat?

- Supportive care
- Altering natural history without curing the disease
- Curing the disease
Need new slide from Ted
MDS patients, n=120

- Relapse
- OS
- EFS

Time in Years

Probability
U.S. treatment approaches to MDS

Overall proportion of recently diagnosed patients (n = 670) and range of established patients across six surveys (n = 3844) taking specific types of therapies at the time of the survey

- **ESA (darbepoetin and/or erthropoietin)**
  - Recently diagnosed patients (proportion): 16%
  - Established patients (range across 6 surveys): 55-63%

- **Azacitidine (Vidaza)**
  - Recently diagnosed patients (proportion): 8%
  - Established patients (range across 6 surveys): 11-15%

- **G-CSF, GM-CSF or peg-filgrastim**
  - Recently diagnosed patients (proportion): 0%
  - Established patients (range across 6 surveys): 8-11%

- **Lenalidomide (Revlimid)**
  - Recently diagnosed patients (proportion): 2%
  - Established patients (range across 6 surveys): 1-9%

- **Decitabine (Dacogen)**
  - Recently diagnosed patients (proportion): 1%
  - Established patients (range across 6 surveys): 0-4%

- **Thalidomide**
  - Recently diagnosed patients (proportion): 1%
  - Established patients (range across 6 surveys): 2-5%

Only 4% of recently dx or established patients were considered for transplant.

Only 1% of recently dx or established patients were enrolled into clinical trials.

Percentage of patients who believed their most current treatment would be curative, in the overall population and according to treatment group and risk group. *30% were uncertain and 54% did not believe that treatment would be curative.
• A chance of cure is better than giving up ...
• … even if it is a small chance...
• … and the risks are high.