Treating Higher Risk MDS

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“Higher Risk” MDS

• Question 1: How do we judge the risk and impact of MDS upon you?

• Question 2: What are the options for higher risk MDS?

• Question 3: How do we decide which treatment to use and when?

What does high risk mean?

• Risk technically refers to “risk” of the illness either becoming fatal or changing to acute leukemia

• We break these down into

  • Low Risk
  • Intermediate (2 levels)
  • High Risk
Factors of Risk

- Blood Counts
  - # Of Lines

- Blasts in Marrow
  - Normal
  - Normal: 3-5% in between MDS and AML
  - AML

- Cytogenetics
  - Normal
  - "Favorable"
  - "Complex"

- Age >65
- "Performance Status"
- "Transfusion Dependence" or WBC < 2,000

MD Anderson Prognostic Scoring System (based on n=958)

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Score</th>
<th>% patients</th>
<th>Median survival (Months)</th>
<th>% alive at 3 years</th>
<th>% alive at 6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-4</td>
<td>16</td>
<td>54</td>
<td>63</td>
<td>38</td>
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<tr>
<td>Int-1</td>
<td>5-6</td>
<td>24</td>
<td>25</td>
<td>34</td>
<td>13</td>
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<tr>
<td>Int-2</td>
<td>7-8</td>
<td>24</td>
<td>14</td>
<td>16</td>
<td>6</td>
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<tr>
<td>High</td>
<td>9-15</td>
<td>36</td>
<td>6</td>
<td>4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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MDS Treatment Choices

- Observation
- Current Medicines
- Experimental Medicine
- Stem Cell Transplant

Risk vs Reward

Stem Cell Transplant

- What is a transplant?
- Who can be the donor?
- What is the process?
- What are the risks?
- Who should have a transplant?

What is a transplant?

- Transplant of another person's marrow into your blood to replace abnormal cells and hopefully lead to normal marrow function
Who can be the donor?

- DONOR = Self (Autologous)
- DONOR = Another (ALLOGENEIC)
- DONOR = IDENTICAL TWIN (Syngeneic)
- DONOR = SIBLING
- DONOR = STRANGER (Matched Unrelated Transplant)
- DONOR = Half Match (Haploidentical)

What is the process?

1. Conditioning
2. Receiving the “transplant”
3. In Hospital recovery
4. Up to day 100
5. Long Term

Conditioning Regimens

Required Contribution of GVT Effect

- BU + CY + TBI
- BU + TBI
- CY + TBI
- FLU + AraC
- BU + CY (± ATG)
- CY + BU
- BU + Melphalan
- FLU + Melphalan
- FLU + Treosulfan
- FLU + BU (3.2-16)
- tbi + FLU (90-250)

*TBI at ≤12 Gy; ≥12 Gy.

Intensity

Bu Deep
Donor/Host Interactions: High Intensity versus Low Intensity Conditioning

What are the risks?
1. Will it cure the MDS?
2. Transfusions
3. Risk of infections
4. Risk of bleeding
5. Risk of impact in organs (liver, lungs)
6. Graft VS. Host Disease

Who should have a transplant?
1. Complex Personal Decision
2. Balanced against “risk” of illness
3. Quality of the donor, your overall health
Medicines for High Risk MDS

• Medicines that treat acute leukemia
• Medicines approved for MDS
• Combination approaches

Medicines that treat acute leukemia

1. “Induction chemotherapy”
   • Cytarabine, Anthracyclines, Etc

2. Low Intensity acute leukemia therapy
Medicines for High Risk MDS

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Medicines approved for MDS

1. Lenalidomide
2. Azacitidine
3. Decitabine
Azacitidine (Vidaza™)
Decitabine (Dacogen™)

1. Both injectable medicines (for now)
2. Either injections under skin or IV
3. Typically for 5-7 days in a row once per month
4. Side effects
   1. Can lower blood counts further
   2. Mild nausea
   3. Injection site reactions
5. After 6 months if a good response we are uncertain best approach for maintenance

Epigenetics and Cancer

Open chromatin; Transcription high
Compacted chromatin; Transcription low

Possible Benefits

1. Best case scenario people live longer
2. Delay movement towards AML
3. Improve blood counts
   1. Less risk of bleeding?
   2. Less impact of anemia?
   3. Less risk of transfusion
AZA-001 Overall Survival: Azacitidine vs “Conventional Care”

Log-Rank, p=0.0001
HR = 0.58 [95% CI: 0.43, 0.77]
Deaths: Azan = 82, Control = 113
Difference: 9.4 months

Decitabine Survival Study (GMDSG-EORTC 06011)

Eligibility:
- Age 60 or older
- MDS or CMML (FAB)
- <11% blasts or <11% blasts with poor cytogenetics or 21-30% blasts with stable disease x 1 month

Supportive care

Primary endpoint:
Overall survival

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NCCN Guidelines: Higher-risk MDS (IPSS Intermediate-2/High)

- High-intensity therapy candidate
- Supportive care for all
- Not a candidate for intensive therapy
- Allogeneic SCT (may use azacitidine or decitabine as "bridge")
  - If relapse: Azacitidine/decitabine or clinical trial
  - Azacitidine (preferred) or decitabine or clinical trial or high-intensity therapy
  - N.R. or relapse: Clinical trial or supportive care

Based on v.2 2010; www.nccn.org

German Prospective Trial: Allogeneic Transplantation vs. Azacitidine

Eligibility:
- MDS IPSS Int-2, High, or int-1 with High-Risk Cytogenetics
- AML with 20-30% blasts
- Age 55-79 and suitable/willing transplant candidate

- 4 cycles of azacitidine; Donor search
  - Progressive disease: off study
  - Stable disease, complete response, or partial response
  - No donor: Continue azacitidine until progression
  - 10/10 matched donor available: Proceed with R.I.C. transplant

Azacitidine Maintenance after Induction Chemotherapy

Eligibility (n=60):
- IPSS Int-2/High MDS (n=17)
- CMML with >10% blasts (n=6)
- Post-MDS AML (n=37)

INDUCTION
Daunorubicin 60 mg/m² IV days 1 and 2
Cytarabine 150 mg/m² IV or SC days 1-7
Could undergo re-induction x 1

* = initial dose of 75 mg/m² reduced to 60 mg/m² due to grade 4 neutropenia

<table>
<thead>
<tr>
<th>CR</th>
<th>No CR</th>
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</thead>
<tbody>
<tr>
<td>n=24 (40%)</td>
<td>n=36 (60%)</td>
</tr>
<tr>
<td>Azacitidine 60 mg/m²* SC x 5 days</td>
<td>Supportive/palliative care</td>
</tr>
<tr>
<td>Repeat every 28 days</td>
<td></td>
</tr>
</tbody>
</table>

Median CR duration: 13.5 months
Median survival: 20 months
Grade ¾ neutropenia/thrombocytopenia: 9.5% and 30% of cycles

Grøvdal M et al Br J Haem 2010; Epub May 20
What Do We Mean by “Quality of Life” (QOL)?

- While QOL is to large extent in the eye of the beholder, it is generally considered to have several domains:
  - Presence and Severity of Symptoms
  - Ability to Function
  - Quality of Interpersonal Interactions
  - Sense of Well-Being
  - Transcendence
  - Physical
  - Social
  - Psychological
  - Emotional
  - Intellectual
  - Spiritual
QOL Research

- Most treatment trials in MDS focus on the “objective” measures of disease activity, and not QOL.
  - If the disease improves, QOL is assumed to follow
  - This may or may not be true!

Net Symptom Burden

Survivorship

“Survivorship”

A definition

- SURVIVORSHIP
- Noun
  - 1. The right of a joint tenant, or other person who has a joint interest in an estate, to take the whole estate upon the death of other.
  - 2. The state of being a survivor.
Webster’s Online Dictionary

- **Survivor**
- **Noun**
  - 1. One who lives through affliction; “the survivors of the fire were taken to a hospital”.
  - 2. One who outlives another; “he left his farm to his survivors”.
  - 3. An animal that survives in spite of adversity; “only the fittest animals were survivors of the cold winters”.

Traditional View of “Survivorship”

Diagnosis
Of a “Cancer”
(i.e. breast, colon, Prostate, etc.)

Therapy

No Therapy

Not a Survivor

Positive Spirit
Promoting Wellness
Loving Support
Being Active

Illness
Being Well

Medical Treatments
- Medicines
- Surgery
- Radiation
- Other

LIVING!
Conclusions

1. Higher risk MDS is of concern because of risk of acute leukemia and worse impact on blood counts

2. Transplant can be curative, but timing and use are a complex issue

3. Medicines can be helpful for advanced MDS

4. A complete understanding of where you stand and your options is key with MDS

Thank You