High Risk MDS and Novel Therapy: What’s on the Horizon?

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Aplastic Anemia & MDS International Foundation
Regional Patient and Family Conference
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Overview

• Refining Prognosis and ‘High’ Risk
• Novel Treatments
• Advances in Stem Cell Transplantation
• Examples from the Lab

Refining Prognosis

Low Blood Counts

71 year-old man with big red cells and low blood counts that developed over the past 6 months.

Normal Range

Way too many cells in the bone marrow
4% blasts in aspirate
Dysplasia in all three cell types
Normal Karyotype (chromosomes ok)

Low Blood Counts

71 year-old man with big red cells and low blood counts that developed over the past 6 months.

Normal Range

International Prognostic Scoring System

### MDA Lower Risk Model

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>LR-IPSS Prognostic Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Age, years</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Platelets, ×10⁹/L</td>
<td>50 - 200</td>
</tr>
<tr>
<td>BM blasts, %</td>
<td>≥ 4%</td>
</tr>
</tbody>
</table>

**Risk Category**
- 1 or 2
- 3 or 4
- ≥ 5

**Survival, months from referral**

25%-33% of patients are in Category 3

The survival of Category 3 patients is similar to that of Intermediate-2 risk patients using the IPSS!

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### Guidelines for Higher Risk MDS

**Goal:** to improve DURATION OF LIFE

- **IPSS:** INT-2, HIGH
- **WPSS:** HIGH, VERY HIGH

**Current Therapies**

**Hypomethylating Agents**

Inhibitors of DNA methyl transferases:

- 5-azacytidine (azacitidine)
- 5-aza-2'-deoxycytidine (decitabine)

Both incorporate into DNA and cause hypomethylation (DEC > AZA)

AZA preferentially causes DNA damage and induces apoptosis

**Azacitidine**

- **AZA-001 Phase III:** AZA vs. Id-ARA-C vs. supportive care
  - OS benefit: + 9.5 mos
  - Time to AML: 17.8 vs. 11.5 mos
  - Ti: 45% vs. 11%

**Azacitidine Response:**

- ORR: ~50%
- CR: ~17%
- Median time to response: 3 cycles (81% by cycle 6)
**Decitabine Phase III Trial**
- Dosed q8h x 3 days per 28 days
- CR: 17%
- CR+PR: 30%

**ADOPT Trial and 3-Schedule Trial**
- Dosed q24h x 5 days per 28 days
- CR: 17%
- CR+PR: 32%

**ORR: 52% (+ heme response)**
- Best response: 50% at 2 cycles

**Major Toxicity:**
- Neutropenia: 31% (FN 11%)
- Thrombocytopenia: 18%

**CR: 17%**
**CR+PR: 30%**

**Outcomes After Azacitidine**

<table>
<thead>
<tr>
<th>Reasons for &quot;Failure&quot; in azacitidine failure study</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>9% didn’t tolerate AZA (69% were not responding, 31% had an initial response)</td>
<td></td>
</tr>
<tr>
<td>55% primary failure (progression in 60%, stable disease without response in 40%)</td>
<td></td>
</tr>
<tr>
<td>36% secondary failure after initial response (best response: CR 20%, PR 7%, HI 73%)</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes after failure**
- Median overall survival for whole cohort post-AZA: 5.6 months
- 2 year survival: 15%
- Favorable factors: female, younger (<60), better risk karyotype, <10% blasts, some response to azacitidine
- Comparison to decitabine failures @ MDACC: median survival 4.3 months, n=87

**Guidelines for Higher Risk MDS**

**Goal:** to improve **DURATION OF LIFE**

**Special Considerations:**
- **Refer for Transplant Early**
  - Even patients in their 70’s can benefit from RIC transplant
- **AZA > DEC (for now)**
  - AZA has been shown to have a survival advantage, DEC has not (yet)
- **Don’t forget Quality of Life**
  - Consider treatment palliative and weigh against patient needs
- **Look for Clinical Trials**
  - Few option after AZA are available and none are approved

**Outcomes After Azacitidine**

- **Subsequent therapy**
  - Allogeneic transplant
  - Investigational therapy (e.g., IMiD, HDACi, other)
  - Intensive cytotoxic therapy (e.g., 3&7)
  - Low-dose chemotherapy (e.g., LDAC, 6-MP)
  - Palliative / supportive care
  - Subsequent therapy unknown

- **Number of patients (%)**
  - Allogeneic transplant 37 (9%)
  - Investigational therapy 44 (10%)
  - Intensive cytotoxic therapy 35 (8%)
  - Low-dose chemotherapy 32 (7%)
  - Palliative / supportive care 122 (28%)
  - Subsequent therapy unknown 165 (38%)

- **Median survival**
  - 19.5 months
  - 13.2 months
  - 8.9 months
  - 7.3 months
  - 4.1 months
  - 3.6 months

**Treatment of Higher Risk MDS**

**We need BETTER therapies!**

**We need MORE therapies!**

**Better Formulations**
Oral Azacitidine

2011 – Oral AZA given 7 days out of 28 is safe and appears effective

2012 – Treating for 14 or 21 days enhances biologic activity and is effective – 34% ORR and 40% transfusion independent

2013 – Phase III Clinical Trial of Lower Risk Transfusion Dependence - should lead to FDA approval

**PROS**
Oral drug that can be taken at home

**CONS**
Gastrointestinal side effects
May take 6-8 cycles to reach maximum response

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**Phase 2 study of SGI-110 in 102 patients with Intermediate or High Risk MDS or CMML**

<table>
<thead>
<tr>
<th>Response Category</th>
<th>60 mg/m² (n=53)</th>
<th>90 mg/m² (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+mCR</td>
<td>10 (18.8)</td>
<td>11 (22.4)</td>
</tr>
<tr>
<td>ORR</td>
<td>14 (26%)</td>
<td>17 (34%)</td>
</tr>
</tbody>
</table>

**Response Category**

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Free Treated (n=53)</th>
<th>Tx Naïve (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+mCR</td>
<td>11 (20.8)</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>ORR</td>
<td>12 (23%)</td>
<td>19 (39%)</td>
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**Highest Well Tolerated Dose**

60 mg/m² daily x 5

**Biologically Effective Dose**

60 mg/m² daily x 5

**New Indications**

**Combination Therapy**

**Approach:** Improve upon existing therapies

**Example:** At least 2 clinic trials in development combine:

**Azacitidine**

+ **Deferasirox (Exjade)**

**Advantage:** drugs are already FDA approved for MDS

*Positive results can quickly change practice!*

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**Take Home Message:** SGI-110 may be useful after AZA failure
Lenalidomide in non-del(5q)

- Transfusion dependent Lower Risk MDS without del(5q) randomized to:
  - Lenalidomide 10 mg daily (n = 160) or Placebo (n=79)
- 26.9% became transfusion independent
- Median response duration of 32.9 weeks
- Being female, prior ESA, and low EPO were factors predictive of response
- Rates of AML progression were similar in both arms

Take Home Message: LEN has activity in non-del(5q) LR MDS

Pipeline of Completely New Drugs

PD1-PDL1 Inhibitors
MAP Kinase Inhibitors
TGF-beta Inhibitors
Neddylation Inhibitors
Indolamine Dioxygenase Inhibitors
p53 Modulators
Hedgehog Inhibitors
Aminopeptidase Inhibitors
RNA Pol I Inhibitors
Anti-CD47 Antibodies

Rigosertib (ON-01910)

PLK1 & Cdc25C Inhibition
Finished Phase III Trial

Multikinase Inhibitor
3-day continuous infusion

Randomized Phase III Study of IV Rigosertib vs. BSC in Higher-risk MDS After HMA Failure

<table>
<thead>
<tr>
<th>Disease</th>
<th>ON 01910</th>
<th>BSC</th>
<th>Number (%) of deaths</th>
<th>Median Follow-up (months)</th>
<th>Median survival (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>199</td>
<td>100</td>
<td>161 (81%)</td>
<td>17.6</td>
<td>8.2</td>
<td>0.67 - 1.16</td>
</tr>
<tr>
<td>3-day infusions</td>
<td>17</td>
<td>5</td>
<td>4 (24%)</td>
<td>17.6</td>
<td>8.2</td>
<td>0.67 - 1.16</td>
</tr>
<tr>
<td>3-day pivotal (1800 mg/d)</td>
<td>13</td>
<td>5</td>
<td>4 (31%)</td>
<td>17.6</td>
<td>8.2</td>
<td>0.67 - 1.16</td>
</tr>
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</table>

Slide borrowed from Dr. Rami Komrokji

Rigosertib after Azacitidine

Slide borrowed from Dr. Rami Komrokji
Raza et al. Blood 2011; 118(22): 3862
**Randomized Phase III Study of IV Rigosertib vs. BSC in Higher-risk MDS After HMA Failure**

<table>
<thead>
<tr>
<th></th>
<th>Rigosertib N = 199</th>
<th>BSC N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of deaths</td>
<td>161 (81%)</td>
<td>81 (81%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>8.2</td>
<td>5.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>6.0 - 10.1</td>
<td>4.1 - 9.3</td>
</tr>
<tr>
<td>Hazard ratio (rigosertib/BSC)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.67 - 1.14</td>
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</table>

**Take Home Message:** Rigosertib is underwhelming after HMA failure, but we don’t have good alternatives either.

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**Hedgehog Inhibitor – Phase II**

Pathway important for stem cells

Several inhibitors in development

Drug PF-04449913
Phase I in AML and MDS had several responders (7/21)

Combination of PF-04449913 and azacitadine is available at UCSD to previously untreated MDS patients.

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**Hedgehog Inhibitors**

**Luspatercept**

TPO mimetics

G-CSF (neupogen)

EPO/ESAs

**Luspatercept**

TPO mimetics

G-CSF (neupogen)

EPO/ESAs
Promoting Red Cell Production

**Luspatercept (ACE-536) and Sotatercept (ACE-011)**

**Immune Based Therapies**

**PD1 and PD-L1 Inhibitors**

Phase I/II Trial will be opening at UCSD in the Fall

**Stem Cell Transplantation**

**Trends in Transplantation**

Goal of Hematopoietic Stem Cell Transplantation:

1. Replace a dysfunction host hematopoietic system with normal, healthy donor marrow.
2. Allow the donor immune system to destroy the abnormal, diseased host cells (MDS).

**Allogeneic Stem Cell Transplantation for MDS**

- <5% of patients with MDS currently undergo allogeneic SCT
- “Only curative therapy”
- Patients who go in to RIC allo SCT with <30% blasts appear to have lower relapse
- Optimal timing, pre-transplant therapy, conditioning unclear; usually reserved for IPSS Int-2/High (IBMTR Markov analysis)

- Survives transplant; MDS cured (35-40%)
- Survives transplant; MDS recurs/persists (30-40%)
- Dies from complication of transplant (20-25%)

Slide borrowed from Dr. David Steensma

Obstacles to Transplantation

Graft Rejection
- need to suppress the host immune system

Toxicity
- infection
- organ damage
- graft versus host disease

Finding a Donor
- siblings match only 25% of the time
- and are often too old or ill to donate

Overcoming Obstacles

Avoiding Graft Rejection
- better approaches to immune suppression

Less Toxicity
- better supportive care
- better antigen matching
- reduced intensity conditioning

Alternative Sources for Stem Cells
- haploidentical – “half” match
- umbilical cord blood stem cells

The potential benefits of allotransplantation using a non-myeloablative regimen

- Low toxicity and mortality
- Low anticipated late effects
- Treatment of elderly patients is feasible
- Suitable for treatment of patients with comorbid conditions
- Can be carried out on an outpatient basis
- Fast recovery with fewer complications and less infection

Trends in Allogeneic Transplants by Transplant Type and Recipient Age*

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Transplant Type</th>
<th>Recipient Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-1996</td>
<td>Related BM/PB</td>
<td>&lt;= 20 yrs</td>
</tr>
<tr>
<td>1997-2003</td>
<td>Unrelated BM</td>
<td>21-40 yrs</td>
</tr>
<tr>
<td>2004-2010</td>
<td>Unrelated PB</td>
<td>41-50 yrs</td>
</tr>
<tr>
<td>2005-2010</td>
<td>Unrelated CB</td>
<td>51-60 yrs</td>
</tr>
<tr>
<td>2007-2010</td>
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<td>&gt; 60 yrs</td>
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* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Allogeneic Transplants for Age > 20yrs, Registered with the CIBMTR, 1993-2010 - by Donor Type and Graft Source -

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Related BM/PB</th>
<th>Unrelated BM</th>
<th>Unrelated PB</th>
<th>Unrelated CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993-94</td>
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<td>1995-96</td>
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<td>1997-98</td>
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<td>1999-00</td>
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<td>2001-02</td>
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<td>2003-04</td>
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<td>2005-06</td>
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<tr>
<td>2007-08</td>
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<tr>
<td>2009-10</td>
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</table>

Genetics and Transplantation

Overall Survival After Transplant

Blasts < 5% (n=42) vs. Blast ≥ 5% (n=45)
Other karyotype (n=59)

Bejar et al. ASH Meeting 2012 (in submission)
Genetics and Transplantation

72 patients with select mutations

Bejar et al. ASH Meeting 2012. (in submission)

Genetic testing can better predict risk of transplantation
Identify patients that are unlikely to do well with standard approaches.
Find those that might do better than expected!

Immune Cell Therapy

Killer T-cell
Plasma B-cell
Tumor Cell
Chimeric Antigen Receptor

TET2
DNMT3A

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And most of – our incredible patients and families!

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Amaan Abidi
Bennett Caughey
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