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

1.9 7.9 45

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

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>LR-IPSS Prognostic Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: years</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>2</td>
</tr>
<tr>
<td>Platelets, ×10^9/L</td>
<td>3</td>
</tr>
<tr>
<td>BM blasts, %</td>
<td>z = 0.05</td>
</tr>
</tbody>
</table>

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!

IPSS-Revised (IPSS-R)

Current Therapies

Guidelines for Higher Risk MDS

Goal: to improve DURATION OF LIFE

NCCN Guidelines’ Version 2.2013 Myelodysplastic Syndromes

Inhibitors of DNA methyl transferases:
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

<table>
<thead>
<tr>
<th>Subsequent therapy</th>
<th>Number of patients (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic transplant</td>
<td>37 (9%)</td>
<td>19.5 months</td>
</tr>
<tr>
<td>Investigational therapy (e.g. IMID, HDAC, other)</td>
<td>44 (10%)</td>
<td>13.2 months</td>
</tr>
<tr>
<td>Intensive cytotoxic therapy (e.g., 3&amp;7)</td>
<td>35 (8%)</td>
<td>8.9 months</td>
</tr>
<tr>
<td>Low-dose chemotherapy (e.g., LDAC, 6-MP)</td>
<td>32 (7%)</td>
<td>7.3 months</td>
</tr>
<tr>
<td>Palliative / supportive care</td>
<td>122 (28%)</td>
<td>4.1 months</td>
</tr>
<tr>
<td>Subsequent therapy unknown</td>
<td>165 (38%)</td>
<td>3.6 months</td>
</tr>
</tbody>
</table>

5% didn’t tolerate AZA (60% were not responding, 31% had an initial response)

53% primary failure (progression in 60%, stable disease without response in 40%)

36% secondary failure after initial response (best response: CR 20%, PR 7%, HI 73%)

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

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
SGI-110

- Resistant to degradation
- Longer half-life
- May allow less frequent dosing
  - 5 days vs. once weekly
- In clinical trials at USC

**Combination Therapies**

**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!

**Lenalidomide + Azacitidine**

- Multicenter, single-arm open-label phase II continuation study (N = 36)
- Patient eligibility
  - Higher-risk MDS: CMML-2, RAEB-1 or -2, IPSS intermediate 2 or high (score ≥ 1.5), or revised IPSS score 4 or 5
  - No previous treatment with lenalidomide or azacitidine
- Maximum of seven 28-day treatment cycles administered
  - Lenalidomide 10 mg on Days 1-21
  - Azacitidine 75 mg/m² on Days 1-5
  - After 7 cycles, patients could continue azacitidine monotherapy off study
- Median patient follow-up: 12 mos (range: 3-55)

**Positive results can quickly change practice!**

**Lenalidomide + Azacitidine**

- Median CR duration: 17+ mos (range: 3-39+)
- Median OS among CR: 37+ mos (range: 7-55+)
- 8 patients evolved to AML at median of 18 mos after CR
- Treatment well tolerated; FN was most common grade 3/4 AE (22%)
**S1117 (US/Canada Intergroup) Study**

Eligible:
- Higher-risk MDS or CMML (25%-29% blasts or 45%-49% blasts)
- Higher-risk MDS or CMML (5-19% blasts or IPSS Int-2/High)

Eligible: Higher-risk MDS or CMML (25%-29% blasts or 45%-49% blasts)
- Azacitidine monotherapy (7 days x 75 mg/m²/day)
- Azacitidine + lenalidomide (10 mg/d for 21/28 days)
- Azacitidine + vorinostat (600 mg/day)

Primary endpoint: overall response rate (ORR) (IWG 2006)
Secondary endpoints: overall and progression-free survival, safety

Power: 81% probability of detecting a 20% difference in ORR (with alpha 0.05)

Pipeline of Completely New Drugs

- Ezatiostat
- 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
Multikinase Inhibitor
Currently in Phase III Trial
3-day continuous infusion

ON 01910

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 decitabine is open and will be available at UCSD to previously untreated MDS patients.

Rigosertib after Azacitidine

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>BM CR (CRh)</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>32</td>
<td>6 (1)</td>
<td>4/10 (31%)</td>
</tr>
<tr>
<td>3-day infusions</td>
<td>17</td>
<td>4 (1)</td>
<td>3/7 (41%)</td>
</tr>
<tr>
<td>3-day pivotal (1800 mg/d)</td>
<td>13</td>
<td>4 (1)</td>
<td>2/6 (33%)</td>
</tr>
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</table>
Ezatiostat (Telintra)

- Stimulates differentiation pathway downstream of growth factor receptors

**Target population are lower risk patients, but trials show activity in heavily pretreated patients!**

**Phase II Study:**
- 56% had previously received Azacitidine or Decitabine
- 38% had previously received Lenalidomide
- 77% had previously received Erythropoietin

**Results:**
- 22% had a red cell response
- 19% had a neutrophil response
- 20% had both
- 29% had reduced transfusion needs
- average time to response was 8 WEEKS!
- very little toxicity!!


Stem Cell Transplantation

<5% of patients with MDS currently undergo allogeneic SCT

"Only curative therapy"

Patients who go in to RIC allo SCT with <10% blasts appear to have lower relapse.

Optimal timing, pre-transplant therapy, conditioning unclear; usually reserved for IPSS Int-2/High (IBMTR Markov analysis)

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).

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*
1990-2010

* 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 -

Genetics and Transplantation

Overall Survival After Transplant

Blasts < 5% (n=35)
Blasts ≥ 5% (n=37)
Other karyotype (n=49)
Complex karyotype (n=23)

p = 0.014
p < 0.001

Genetics and Transplantation

72 patients with select mutations

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 (n = 14)</td>
<td>3.90 (1.85, 8.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DNMT3A (n = 14)</td>
<td>3.54 (1.45, 8.64)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Overall Survival After Transplant

- TP53 and DNMT3A Mut Absent (n=14)
- TP53 or DNMT3A Mut Present (n=26)

Gene 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!

### Immunologic Therapy

**Killer T-cell**

**Tumor Cell**

**Plasma B-cell**

**Chimeric Antigen Receptor**

Immunologic Therapy

Chimeric Antigen Receptor

Modified T-cell

Tumor Cell

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