MDS clinical research priorities

- More accurate diagnosis
  - Current techniques are to some extent subjective
- Better prognostication
  - There are limits to this, but helps decide on therapy
- Improved therapy

Largest unmet therapeutic needs

- Increase proportion of aza/decitabine responders
  - Need to increase also depth of response
- Treatments for patients after aza/decitabine stop working
- Treatments for "higher" lower risk patients
  - Defined by molecular genetics or other features
- Who else does lenalidomide work for besides people with del(5q)?
- Other curative therapies besides transplant

Outcomes in MDS after hypomethylating agent failure

Reasons for "failure" in azacitidine failure study

- 9% didn’t tolerate Aza (69% were not responding, 31% had an initial response)
- 55% 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
- Median overall survival for whole cohort post-azacitidine: 4.3 months, n=87
- Comparison to decitabine failures @ MDACC: median survival 4.3 months, n=87

Need for additional therapeutic options in MDS - Outcomes after azacitidine / decitabine failure are poor

- Data available on 435 pts
  - from AZA001, J9950, J0443, French compassionate program
- Overall median survival after azacitidine failure: 5.6 months

<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, HDACi, other)</td>
<td>44 (20%)</td>
<td>13.2 months</td>
</tr>
<tr>
<td>Intensive cytotoxic therapy (e.g., 3+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>

Prebet T et al / Clin Oncol 2011; 29:3322-7
Jabbour E et al Cancer 2010;116(16):3830-4
Options when azacitidine or decitabine fail to produce a response, or after an initial response is lost...

- Switch to the other hypomethylating agent
- [0 responses in 17 pts in GFM series, lost 10-40% in MoUfitt]
- Continue the current therapy anyway, with or without adding a second agent (e.g., deacetylase inhibitor) – may delay progression
- Supportive care only – feels like “giving up”
- Clinical trial enrollment – lots of trips to major center
- Off-label therapy (e.g., low-dose cytarabine, clofarabine) – doesn’t work very well overall
- Allogeneic stem cell transplant – only a few pts eligible

New nucleoside analogues

- **SGI-110**: second-generation hypomethylating agent
  - dinucleotide of decitabine and deoxyguanosine
  - delivered as a subcutaneous injection
  - allows a longer half-life and more extended decitabine exposure
- 15 pts with Int-2/High risk MDS
  - Median age 74; all had previous aza/decitabine
  - 5 responders (33%), duration 28-224 days
  - Most common AE: injection site pain, diarrhea

ON01910.Na (rigosertib) - multikinase inhibitor

- **Cell-cycle functions and localizations of Plk1**
- **ON 01910.Na**
  - Multikinase inhibitor
  - Polo-like kinase 1 modulator?
  - P38Abl/Akt/ERK pathway inhibitor
  - Induces Bim, inhibits Mcl-1 activation
  - Reduces cyclin D1 levels

Rigosertib after Azacitidine

- **Primary Endpoint:**
  - Overall survival
- **Secondary Endpoints:**
  - IWG 2006 response
  - AEs, etc

Rigosertib (ON01910.Na) randomized trial for post-HMA failure

- **Eligible patients:**
  - MDS (FAB) with 5-30% blasts and at least one cytopenia; WBC < 25x10^9/L
  - No response or progression after 26 cycles azacitidine or 24 cycles decitabine
  - Not an allogeneic stem cell transplant candidate, or refused transplant
  - No low-dose cytarabine within last 2 years
  - Bilirubin <1.5 and creatinine <2 mg/dL

Oral rosiglitaz for lower-risk patients

- 34 evaluable patients
  - Transfusion dependent, IPSS Low/Int-1 MDS
  - 8 got continuous dosing, 26 intermittent
- Of intermittent dosing, 50% became transfusion independent
  - For 2 pts, this lasted >9 months
- Urinary adverse events most common
  - Urgency/frequency 38%
  - Dysuria 15%
  - Hematuria 15%
  - More common with continuous dosing
Genetic Predictors of Response
Analysis of MDS patients treated with stem cell transplantation or hypomethylating agents

Rafael Bejar MD, PhD
Kristen E. Stevenson MS
Petar Stojanov
J. Eric Zawel
Michal Bar-Natan MD
Bennett Caughley
Hui Wang PhD
Guillermo Garcia-Manero MD
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Rui Chen PhD
Donna S. Neuberg ScD
Benjamin L. Ebert MD, PhD

ASH Oral Presentation
December 10th, 2012

SCT Cohort – Treatment Outcomes

HM Cohort – Mutations & Response

MDS Cohorts and Sequencing Methods

Targeted the coding regions of 74 genes including 42 known to be mutated in MDS

Stem Cell Transplant Cohort
HaloPlex PCR

Hypomethylating Agent Cohort
48-plex sheared DNA libraries

Illumina Hiseq 2000
Realignment and Analysis using GA4R pipeline at the Broad Institute

MDS Patients – Hypomethylating Rx

213 MDS patients Treated with Hypomethylating Agents (aza, decitib - HM Cohort)

Exclusions: AML before treatment - no DNA sample available - other heme malignancy

Demographics: 73% were male - 48% were 70 years old or more

Efficacy and Safety of Eltrombopag
for the treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk MDS:
Preliminary Results of a Prospective, Randomized, Single-Blind Placebo-Controlled Trial
Oliva for the EQol-MDS – ASH December 2012
**Patients**

(N = 69)

- Phase II, national, multicentre, prospective, randomized, single-dose start: 50 mg with increases every 2 weeks up to 300 mg daily.

**Results:** PLT counts at 16 weeks

<table>
<thead>
<tr>
<th>Response</th>
<th>Eltrombopag N=9</th>
<th>Placebo N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, n</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Complete Response, n</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NR</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>8 (89)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>WHO bleeding grade ≥ 2, events</td>
<td>0</td>
<td>8*</td>
</tr>
</tbody>
</table>

**Time to Response:**
- In 4 cases, early responses after 1 week;
- In 2 cases by 8 weeks and in 2 cases by 12 weeks.

Median daily eltrombopag dose at response was 75 mg (IQR 50-175 mg).

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**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!

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**Lenalidomide + Azacitidine**

- Multicenter, single arm open-label phase II continuation study (N = 36)
- Patient eligibility
  - Higher-risk MDS: CMML-2, RAE-A1 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)

**Slide borrowed from Dr. Rami Komrokji**

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
- ECOG 2 or below or WBC <3.5 x 10^9/L

Primary endpoint: overall response rate (ORR) (9WG 2006)
Secondary endpoints: overall and progression-free survival, safety

Principal investigator: Mikkael Sekeres, Cleveland Clinic

Azacitidine + Vorinostat

Eligibility
- Age ≥ 18 years
- Untreated MDS (p int-1) or AML
- And any of the following:
  - Total bilirubin ≥ 2 mg/dl
  - Creatinine ≥ 2 mg/dl
  - ECOG performance status ≥ 2
- Excluded from all other clinical trials:
  - Presence of other active malignancy

Dose and schedule
- Aza 75 mg/m² IV QD days 1 to 5
- Vorinostat 200 mg PO TID days 1 to 5
- Cycles repeated every 28 days

<table>
<thead>
<tr>
<th>Patients (N=30)</th>
<th>CR (%)</th>
<th>CRp (%)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>8 (26)</td>
<td>1 (3)</td>
<td>30</td>
</tr>
<tr>
<td>Diploid (7)</td>
<td>3 (42)</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>-S/ -7 (16)</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>13</td>
</tr>
<tr>
<td>-8 (3)</td>
<td>2 (66)</td>
<td>0</td>
<td>66</td>
</tr>
</tbody>
</table>

Immune Reconstitution after Stem Cell Transplantation

- Promising areas for translational research
  - Develop new ways to enhance reconstitution of donor stem cells to reduce the risk of infection
  - Develop new approaches to manipulate the immune system to prevent and treat GVHD
  - Develop new methods to enhance graft-versus-leukemia (GVL) and reduce the risk of relapse after transplant

Immune Reconstitution after Stem Cell Transplantation

- Develop methods to isolate virus-specific T cells from stem cell transplant donors
  - e.g. Anti-CMV, anti-EBV
- Monitor immune reconstitution in transplant patients to identify mechanisms of immune tolerance
- Develop bio-engineered leukemia vaccines to enhance GVL

GVAX: GM-CSF Secreting Tumor Cell Vaccine

- Collect MDS cells prior to transplant
- In the laboratory, treat the sick MDS cells to make them a target for the donor’s immune system (GM-CSF transduction)
- Generate vaccine
- Give vaccine after transplant to reduce risk of relapse
- Trials ongoing...
If I can help...

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