Therapies For MDS: Where Are We Going?

David Steensma, MD FACP
Associate Professor of Medicine, Harvard Medical School
Adult Leukemia Program, Dana-Farber Cancer Institute
Hematological Oncology Service, Brigham & Women’s Hospital

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11/3/2014

Disclosures

Data monitoring committee: Amgen
Scientific advisory board: Genoptix, Celgene, Boehringer Ingelheim,
Off-label / experimental use: only azacitidine, decitabine and lenalidomide are FDA approved for MDS

How Are Patients With MDS Treated In November 2014?

Hypomethylating agents / DNA methyltransferase inhibitors / epigenetic drugs
Azacitidine (Vidaza ®) Approved May 2004
Decitabine (Dacogen ®) Approved May 2006

Iron chelators
Deferasirox (Exjade ®) Approved November 2005

Blood cell (hematopoietic) growth factors
Epoetin alfa (Procrit ®)
Darbepoetin alfa (Aranesp ®)
Filgrastim, G-CSF (Neupogen ®)
Pegfilgrastim (Neulasta ®)

Platelet growth factors
Romiplostim (NPlate ®)
Eltrombopag (Promacta ®)

Immunosuppressive drugs (ATG, CsA)

Immunomodulatory drug (IMID)
Lenalidomide (Revlimid ®) Approved December 2005

Supportive care for all (transfusions and antimicrobials PRN, iron chelation)

Cytopenia(s)
Disease feature
First-line therapy
Anemia only
Del (5q)
Lenalidomide
No del(5q), sEPO <500
ESA ± G-CSF
Neutropenia or thrombocytopenia or both
None established; observation, growth factors, aza/decit reasonable

Higher-risk MDS

Allogeneic SCT candidate?
Therapeutic approach
Yes
Proceed to transplant ASAP; a hypomethylating agent (HMA) or cytotoxic chemotherapy may be useful as a "bridge"

No
Azacitidine; decitabine as alternate

Partly based on 2014 NCCN guidelines; see www.nccn.org

What Are The Greatest Needs In The MDS Field?
MDS clinical research priorities

- More accurate diagnostic methods
  - Current techniques are to some extent subjective
  - Molecular testing is helping in ambiguous cases
- Better prognostication
  - There are limits to this, but helps decide on therapy
- Better systems of health care delivery
  - In the US we use our health care dollars poorly / inefficiently
- Improved therapy

Largest specific unmet therapeutic needs

- Increase proportion of aza/decitabine responders
  - Current complete response rate 10-20%
  - Current overall response rate 40-50%
  - Average duration of response 8-11 months
  - Need to increase also depth of response and duration
- 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 after azacitidine or decitabine failure of patients with MDS

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
- 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

Outcomes after azacitidine or 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, 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>

Subsequent therapy unknown

- Switch to the other hypomethylating agent (0 responses one European series, but 19-40% in H. Lee Moffitt series)
- 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

Why Has Therapy of MDS Been So Challenging?
Unlike leukemia, there are no widely useful MDS “cell lines”. Several animal models now exist, but may not be representative. This makes screening targeted agents more challenging.

MDS mutation landscape: Obvious targets are few

Proliferation

Epigenetic regulation

Impaired Differentiation

Pre-mRNA splicing

Targetable mutation

Despite that, there are many new agents in development...

Challenge #1 to narrowly targeted therapies

Challenge #2 to developing narrowly targeted therapies

Challenge #3 to narrowly targeted therapies

Long “tail” of lesions present at >2% level

Challenge #4 to narrowly targeted therapies

Painful.

Impact of Cancer Research Bureaucracy on Innovation, Costs, and Patient Care

Journal of Clinical Oncology

Table 1: Agents in development for MDS in clinical trials that are active, including patients

| Agent | Development Status | Activity
|-------|--------------------|--------|
| Enasidenib | Phase 2 | Active
| Idasanutlin | Phase 2 | Active
| Azacitidine | Phase 3 | Active
| Decitabine | Phase 3 | Active
| RDW-1440 | Phase 1/2 | Active
| Rigosertib | Phase 1/2 | Active
| AG-120 | Phase 1 | Active
| GPR178 | Phase 1 | Active
| BAY 14-9450 | Phase 1 | Active
| MDM2 antagonist | Phase 1 | Active
| JAK1/2 inhibitor | Phase 1 | Active
| BET inhibitor | Phase 1 | Active
| EZH2 inhibitor | Phase 1 | Active
| TET2 inhibitor | Phase 1 | Active
| TET2 activator | Phase 1 | Active
| TET2 expression | Phase 1 | Active

Surel and Steensma, Blood 2014
Really, a lot! (But not all agents are created equal)

Predicting the future accurately is notoriously difficult. Where are our robot housekeepers, rocket trains, and flying cars?!

Some themes

- Combination therapies – lots of “aza plus” studies ongoing or getting going
- Increased use of targeted therapies (even if targets not entirely understood)
- Using old drugs in new ways (e.g., oral formulations of azacitidine and decitabine, altered schedules)
- Greater use of allogeneic stem cell transplant – expanded donor pool and stem cell source options, bioengineered cellular products, older patients

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 28-222 days
  - Most common AE: injection site pain, diarrhea

Rigosertib after Azacitidine

<table>
<thead>
<tr>
<th></th>
<th>IT</th>
<th>BM-CR (%)</th>
<th>IT</th>
<th>OS (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>32</td>
<td>6 (1)</td>
<td>4</td>
<td>10/32 (31%)</td>
</tr>
<tr>
<td>3-day infusions</td>
<td>17</td>
<td>4 (1)</td>
<td>3</td>
<td>7/17 (41%)</td>
</tr>
<tr>
<td>3-day pivotal (1800 mg/d)</td>
<td>13</td>
<td>4 (1)</td>
<td>2</td>
<td>6/13 (46%)</td>
</tr>
</tbody>
</table>

Slide borrowed from Dr. Rami Komrokji

O’Connell C et al, EHA 2013, abstract P189
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 ≥6 cycles azacitidine or ≥4 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

ON 01910.Na 1800 mg/24 hr as a 72-hr continuous infusion on Days 1, 2, and 3 of a 2-week cycle

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

Best Supportive Care (BSC) or Low-Dose Cytarabine (LDAC)

Randomize 2:1

n=180

n=90

8 months median survival

6 months median survival

Oral rigosertib 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

Raza A ASCO 2013 Abstract 7031

Eltrombopag vs Placebo in IPSS Low- or Intermediate-1 Risk MDS and low platelet count receiving supportive care

- Phase II, national, multicentre, prospective, randomized, single-blind study for patients with plt ct <30

Randomization 2:1 Wk 24

Patients (N = 69)

Dose start: 50 mg with increases every 2 weeks up to 300 mg daily.

Platelet responses 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 eltrombopag at response was 75 mg (IQR 50-175 mg).

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 Trial

- 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/m^2 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 (≥ 10% blasts or acute-ML)
- **Power:** 83% probability of detecting a 20% difference in ORR (with alpha 0.05)

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

**Principal investigator:** Mikkael Sekeres, Cleveland Clinic

**Azacitidine + Vorinostat combination trial in sicker patients**

**Eligibility**

- **Age ≥ 18 years**
- Untreated MDS (≥ Int-2) 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

**Patients (N=30)**

<table>
<thead>
<tr>
<th></th>
<th>CR (%)</th>
<th>CRp (%)</th>
<th>ORR (%)</th>
</tr>
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<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>-5/-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>
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**Constitutive Activation of TGF-β Signaling Suppresses Hematopoiesis in MDS**

**Previous attempts**

- TNF alpha antagonists such as those approved for autoimmune conditions (etanercept, infliximab)
- Pentoxifylline/ciprofloxacain/dexamethasone
- Thalidomide
- Amifostine [thiophosphate free radical scavenger] (0 responses in Mayo trial)
- Siltuximab [anti-IL6 antibody] (2011-2012 75 patient randomized trial, 0 responses)

**Altering the cytokine milieu**

- Fields et al. Expert Opin. Investig. Drugs (2013) 22(1)
ACE-011 (Sotatercept)

- high affinity ActRIIA receptor fusion protein which acts as a "ligand trap"
- sustained inhibition of Activin-A & TGF-β superfamily ligand

ACCELERON Pharma

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 Zaremba
Michal Bar-Natan MD
Bennett Caughey
Hui Wang PhD
Guillermo Garcia-Manero MD
Hagop M. Kantarjian, MD

Ash Oral Presentation
December 10th, 2012

Ongoing Randomized Phase II Study of Sotatercept (ACE-011) in Lower Risk MDS

<table>
<thead>
<tr>
<th>Dose Finding Phase Sotatercept</th>
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</thead>
<tbody>
<tr>
<td>Eligibility</td>
</tr>
<tr>
<td>- Low/Int-1</td>
</tr>
<tr>
<td>- WHO MDS</td>
</tr>
<tr>
<td>- MDS/MPN</td>
</tr>
<tr>
<td>- Hgb&lt;9g/dl</td>
</tr>
<tr>
<td>n=20</td>
</tr>
<tr>
<td>0.5 mg/Kg SC q 21 d</td>
</tr>
<tr>
<td>n=20</td>
</tr>
<tr>
<td>1 mg/Kg SC q 21 d</td>
</tr>
<tr>
<td>n=20</td>
</tr>
<tr>
<td>2 mg/Kg SC q 21 d</td>
</tr>
</tbody>
</table>

Endpoints:
- HI-E (IWG 2006)
- HI-E duration
- Progression

Indications for Hematopoietic Stem Cell Transplants in the US, 2011

- Allogeneic (Total N=7,892)
- Autologous (Total N=12,047)

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 shored DNA libraries

Realignment and Analysis using GATK pipeline at the Broad Institute

What About Stem Cell Transplant And Immunotherapy?
SCT Cohort – Treatment Outcomes

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

TP53 and DNMT3A Mut Present (n=26) vs TP53 and DNMT3A Mut Absent (n=46) 

Overall Survival After Transplant

- Primary 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

Adaptive Immnotherapy

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...

david_steensma@dfci.harvard.edu
or
dsteensma@partners.org

(617) 632-3712
Thank you!

DFCI Adult Leukemia Clinical Program:
- Richard Stone MD
- Daniel DeAngelo MD PhD
- Martha Wadleigh MD
- Gregory (Goyo) Abel MD MPH (pop sci)
- R. Coleman Lindsko MD PhD (translational)

Sarah Cahill PA-C
Katherine Edmonds NP
Adriana Penicaud PA-C
Susan Buchanan PA-C
Ilene Gailinsky NP &
Clinical Research Coordinators
Regulatory Team

Dana-Farber Cancer Institute
Harvard Medical School quadrangle