Therapeutic options after first line treatment failure

Orlando ASH 2015

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I have no relevant financial relationships to disclose.
What are the major needs in MDS? (problems that limit significant cure rate)

- Identification of poor prognosis “lower risk” patients
  - By default sparing patients with no need of therapy
  - Concept of early intervention
- Development of new targeted therapies for patients with lower risk MDS
- Development of new therapies for patients with higher risk MDS
- Understanding mechanisms of resistance to epigenetic modulators in MDS
- Understanding mechanisms of transformation to AML
- Incorporation of alloSCT in MDS
- Minimizing risk of relapse post alloSCT in MDS
Natural history of MDS after incorporation of HMAs

Prodrome

LR-MDS
- Untreated HMA?
- lenalidomide

HMA failure?

HR-MDS
- Untreated HMA
- AML-like
- SCT

HMA failure
AML-like?

AML

HMA lower risk failure survival: 14-17 months
HMA higher risk failure survival: 4-6 months

H3K4me3 Chip-seq Strategy in MDS

MDS patient’s BM

CD34+

CD34-

Ch-IP with H3K4-3Me Antibody

Control BM

CD34+

CD34-

Solexa Sequencing of Specific H3K4-3Me Rich Chromatin Fragments

Bio-info analysis

MDS specific biomarkers
(Potential Specific Epigenetic Change in MDS)

Wei. Leukemia 2013.
H3K4m3 CHIP-Seq: Data Analysis & Validation

criteria for MDS specific H3K4me3 “peak” selection
• +/- 2kb to TSS of a known gene
• MDS vs control > 3 fold
• p value < 10^-6

Wei. Leukemia 2013.
H3K4me3 Associated Gene Activation in CD34+ Cells of MDS

Wei. Leukemia. 2013
H3K4me3-associated Gene Activation in MDS CD34+ Cells targets an Innate Immunity Like Pathway

Ingenuity Pathway Analysis predicted NFkB-centered signal activation

= with reported involvement in innate immune signaling activation

Wei. Leukemia. 2013
Overexpression of Other Innate Immunity Like Signaling Components in MDS BM CD34+ (non-CHIP-Seq identified)

Genes examined in MDS BM CD34+ cells
TLR1, 2, 3, 4, 6, 7, 8, 9, MYD88, IL-8

expression level in primary MDS BM CD34+ cells

Genes showing potential prognostic value
TLR1 and MYD88 expression levels negatively associate with overall survival (OS) in MDS patients

Wei. Leukemia. 2013
TLR2 Stimulation Activates Histone Demethylase JMJD3

De Santa F et al. Cell 2007

JMJD3 is Overexpressed in MDS CD34+ Cells

Wei. Leukemia. 2013
Innate Immunity Genes & Patient Response to Epigenetic Targeting Drugs

SAHA/ AZA

TLR6

C5AR1

FPR1

FPR2

TYROBP

Yang H et al
Cellular Immune Dyregulation in MDS

Immunosuppression

- CTL ↓
- Th17 ↓
- Tregs ↑
- DC ↓
- Macrophage ↓
- Adaptive Immune Responses B Cells ↓
- NK ↓

Selective Leukemic Clone Growth

Tumor Immune Evasion Mechanisms:
1. Inhibitory B7 expression by tumor, APC and stroma cells.
2. APC
3. Treg.
What about cellular immunity?
Aberrant up-regulation of PD-L1, PD-L2, PD-1 and CTLA4 in CD34+ cells from MDS, CMML and AML.

Yang et al Leukemia 2014
Dynamics of PD-L1, PD-L2, PD-1 and CTLA4 expression in patients treated with different forms of epigenetic therapy.

Yang et al Leukemia 2014
Epitargeting of immune pathways in MDS

1. Molecular Mechanisms: Interaction between innate immune signal and other genetic lesions in MDS pathogenesis

2. Molecular Mechanisms: Searching endogenous PAMP/DAMP that activates innate immune signaling and involves in MDS pathogenesis

3. Evaluate Therapeutic Potential of targeting innate immune signaling in MDS

Gomez-Ganan. Leukemia 2015.
Adult murine hematopoiesis

**HSC COMPARTMENT** = **KSL**

**MYELOID PROGENITOR COMPARTMENT** = **KL**

**LYMPHOID PROGENITOR COMPARTMENT**

- **LT-HSC**
  - Lin^-kit^+sca1^+CD34^-CD135^-
- **ST-HSC**
  - Lin^-kit^+sca1^+CD34^-CD135^-
  - Lin^-kit^+sca1^+CD34^-CD135^+
- **MPP**
  - Lin^-kit^+sca1^+CD34^-CD135^+
  - Lin^-kit^+sca1^+CD34^-CD135^bright
- **CMP**
  - Lin^-kit^+sca1^-CD34^-CD16/32^-
  - Lin^-kit^+sca1^-CD34^-CD16/32^+
- **GMP**
  - Lin^-kit^+sca1^-CD34^-CD16/32^+
- **MEP**
  - Lin^-kit^+sca1^-CD34^-CD16/32^-
- **LMPP**
  - Lin^-kit^+sca1^-CD34^-CD135^+

**ERYTHROCYTES**

**PLATELETS**

**GRANULOCYTES**

**MONOCYTES**

**PRO T-CELL**

**PRO B-CELL**

Modified from Iwasaki H et al. Immunity 2007
Short-term in TERT-ER mice: effect Aza on CBC

Effect of 7-day AZA treatment on WBC counts in TERT-ER mice

Effect of 7-day AZA treatment on neutrophil counts in TERT-ER mice

Effect of AZA treatment on hemoglobin levels in TERT-ER mice

Effect of 7-day AZA treatment on platelet counts in TERT-ER mice

Colla. Cancer Cell 2015; Gomez-Ganan poster 2852 Sunday
Short-term in TERT-ER mice: effect Aza on HSPC

Colla. Cancer Cell 2015; Gomez-Ganan poster 2852 Sunday
Genomics of MDS

Clonal Progression from Myelodysplastic Syndrome (MDS) to Secondary Acute Myeloid Leukemia (sAML).

Flt3 alterations in MDS

Daver et al. AJH 2013
Effect of acquisition of Flt3 or Ras mutations in MDS

Takahashi. Leukemia 2014
5AZA + Sorafenib – Outcomes and Survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=37 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. cycles received, [Range]</td>
<td>3, [1 – 18]</td>
</tr>
<tr>
<td>Median follow-up in weeks, [Range]</td>
<td>24, [5 – 71]</td>
</tr>
<tr>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>6 (16)</td>
</tr>
<tr>
<td>CRI</td>
<td>10 (27)</td>
</tr>
<tr>
<td>PR</td>
<td>1* (3)</td>
</tr>
<tr>
<td>NR</td>
<td>18 (49)</td>
</tr>
<tr>
<td>Died</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Median no. cycles to response, [Range]</td>
<td>3, [1 – 4]</td>
</tr>
<tr>
<td>4-week mortality</td>
<td>1 (3)</td>
</tr>
<tr>
<td>8-week mortality</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

46%
Lower risk non-HMA failure
Results: AML-Free Survival by CyR in Patients With Isolated del(5q) and del(5q) + 1 Additional Abnormality

For the risk of AML transformation or death, CyR was associated with a 41% reduction (95% CI 0.38–0.92; \( P = 0.019 \)) in patients with isolated del(5q) and a 58% reduction (95% CI 0.17–1.02; \( P = 0.056 \)) in patients with del(5q) + 1 additional abnormality, compared with no CyR.

Low dose DAC in LR MDS: Transfusion Independence Rate

<table>
<thead>
<tr>
<th></th>
<th>Arm A (Daily) N(%)</th>
<th>Arm B (Weekly) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RBC Transfusion Independence</strong></td>
<td>20 (62.5)</td>
<td>15 (68.2)</td>
</tr>
<tr>
<td><strong>Platelet Transfusion Independence</strong></td>
<td>22 (68.8)</td>
<td>18 (81.8)</td>
</tr>
<tr>
<td><strong>RBC/PLT Transfusion Independence</strong></td>
<td>20 (62.5)</td>
<td>13 (59.1)</td>
</tr>
</tbody>
</table>

Garcia-Manero JCO 2013
## Phase 1 Oral Aza Study

### Response to Therapy (N=41)

**Garcia-Manero JCO 2011**

<table>
<thead>
<tr>
<th>Disposition</th>
<th>MDS (N=29)</th>
<th>CMML (N=4)</th>
<th>AML (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Ongoing</td>
<td>8 (28)</td>
<td>2 (50)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Terminated</td>
<td>21 (72)</td>
<td>2 (50)</td>
<td>6 (75)</td>
</tr>
</tbody>
</table>

### Median duration of oral therapy, # of cycles, (range)

<table>
<thead>
<tr>
<th></th>
<th>MDS 6.0 (1–23+)</th>
<th>CMML 7.0 (3–17+)</th>
<th>AML 4.5 (1–14+)</th>
</tr>
</thead>
</table>

### Cycle 7 Response Assessment*  

<table>
<thead>
<tr>
<th></th>
<th>MDS 13 (45)</th>
<th>CMML 2 (50)</th>
<th>AML 2 (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR / PR / HI</td>
<td>4 (31)</td>
<td>1 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (61)</td>
<td>1 (50)</td>
<td>2 (100)†</td>
</tr>
<tr>
<td>Progression</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* IWG 2003 or 2006

†Subjects did not meet criteria for progression or response by IWG 2003
Lower risk HMA failure
LR MDS post HMA Failure. Outcome

- Median follow-up: 16 (1-80) months
- Median TFS and OS: 15 and 17 months

Jabbour et al Cancer 2015

<table>
<thead>
<tr>
<th>n</th>
<th>events</th>
<th>mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>290</td>
<td>204</td>
<td>15</td>
</tr>
<tr>
<td>290</td>
<td>201</td>
<td>17</td>
</tr>
</tbody>
</table>
Dual Inhibition of p38 and Tie2 by ARRY-614

p38 MAPK in MDS
- Stress/Inflammatory Stimuli (Cytokines, Hypoxia, FasL)
- Major regulator of the cellular pathways which sense stress
- Over-activated, leading to inappropriate production of myelosuppressive cytokines


Tie2 in MDS – Emerging Target
- Dysregulated, may be a survival factor for AML blast
- Increased signaling associated with poor prognosis

- TNF-α, IL-6, Chemokines
- Decreased RBC, WBC, platelets
- Pleiotropic effects on Progenitors and AML blasts

Ang-1
Ang-2
ARRY-614 Prior Therapies

N = 71
Median prior therapies: 3 (range 0-6; 5 pts with no prior MDS therapies)

‡ATG and/or prednisone
†includes cyclosporine, cytarabine, valproic acid, cladribine, mitoxantrone, rituximab, dexamethasone
*includes siltuximab, HDAC inhibitors, hedgehog inhibitor, TXA127,

Epitargeting of immune pathways in MDS

1. Molecular Mechanisms: Interaction between innate immune signal and other genetic lesions in MDS pathogenesis

2. Molecular Mechanisms: Searching endogenous PAMP/DAMP that activates innate immune signaling and involves in MDS pathogenesis

3. Evaluate Therapeutic Potential of targeting innate immune signaling in MDS

Gomez-Ganan. Leukemia 2015.
Higher risk HMA failure
Outcome in MDS post hypomethylating failure

Disease status after decitabine:  
- MDS: 65 alive, 55 dead  
- AML: 22 alive, 19 dead  
- Total: 87 alive, 74 dead  

$p = 0.29$
Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib vs Best Supportive Care in Patients with Higher-risk Myelodysplastic Syndrome After Failure of Hypomethylating Agents (ONTIME Trial of ON 01910)

ONTIME Trial: Primary Efficacy Results – ITT

Medians:
- RIG 8.2 mo
- BSC 5.9 mo

Stratified log-rank P = 0.33
HR = 0.87 (95% CI: 0.67-1.14)

At risk
- RIG
  - 199
  - 157
  - 114
  - 86
  - 52
  - 29
  - 11
  - 7
  - 4
  - 3
  - 1

- BSC
  - 100
  - 71
  - 47
  - 35
  - 19
  - 14
  - 8
  - 3
  - 2
  - 1

ASH 2014
ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment

Per Prebet 2011, “Primary HMA Failure” was defined as either no response to or progression during HMA therapy

ASH 2014
Clofarabine Plus Low-Dose Cytarabine For The Treatment Of Patients With higher-Risk Myelodysplastic Syndrome Who Have Relapsed Or Are Refractory To Hypomethylating Agent


Department of Leukemia at MD Anderson Cancer Center Houston, Texas

ASH 2014
CLO and LDAC in HR MDS post HMA. Response (N=61)

<table>
<thead>
<tr>
<th>Best Response</th>
<th>N (%); Median [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>9 (14)</td>
</tr>
<tr>
<td>CRp</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hematologic improvement</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>27 (44)</td>
</tr>
<tr>
<td># Cycles to best response</td>
<td>1 [1-7]</td>
</tr>
<tr>
<td>Early death</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

ASH 2014
# CLO and LDAC in HR MDS post HMA. MVA for Response and Survival

## Multivariate analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P</td>
</tr>
<tr>
<td>Cyto Complex vs. No</td>
<td>5.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Plt ≤30 vs. &gt;30</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>PS ≥2 vs. &lt;2</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Response vs. Non-Response</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Prior response to HMA</td>
<td>NA</td>
<td>NS</td>
</tr>
</tbody>
</table>

ASH 2014
CLO and LDAC in HR MDS post HMA. Survival by Response Status

Survival Probability

<table>
<thead>
<tr>
<th>Total</th>
<th>Died</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>Non-Responder</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

ASH 2014
Aberrant up-regulation of PD-L1, PD-L2, PD-1 and CTLA4 in CD34+ cells from MDS, CMML and AML.

Yang et al Leukemia 2014
Examples of clinical trial options

- Genomic annotation: IDH1, IDH2, RAS, Flt-3
- PD1/PDL1 combinations
- Toll-like receptor inhibitors (OPN-305)
- Oral azacitidine (CC-486)
- Bortezomib
- Omacetaxine
- FF-501
Guillermo Garcia-Manero

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