Predicting MDS Response to Drug Therapies Based on a New Method of Interpreting the MDS Mutanome

Cindy Medina, Leylah Drusbosky, Myron Chang, Shireen Vali, Ansu Kumar, Neeraj Kumar Singh, Taher Abbasi, Mikkael Sekeres, Mar Mallo, Francesc Sole, Rafael Bejar, Christopher R. Cogle

University of Florida, Gainesville, FL, USA
CellWorks Group, Inc., San Jose, CA, USA
Cleveland Clinic, Cleveland, OH, USA
Josep Carreras Leukaemia Research Institute, Barcelona, Spain
University of California San Diego, San Diego, CA, USA
General Approach to MDS

MDS Patient

Cytogenetics
FISH
Targeted Gene Sequencing

Clinical Outcomes
• Efficacy
• Safety
• Survival

Treatment:
• HMA
• Lenalidomide
# Biomarkers For Drug Response in MDS

## HMAs

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT doubling after first cycle</td>
<td>Abnormal karyotype</td>
</tr>
<tr>
<td><em>TET2</em> mutation and favorable cytogenetics</td>
<td>Complex karyotype</td>
</tr>
<tr>
<td>No abnormalities in Chr. 5 or 7</td>
<td><em>TP53</em> mutation</td>
</tr>
<tr>
<td><em>TET2</em> mutation with WT <em>ASXL1</em></td>
<td><em>PTPN11</em> mutation</td>
</tr>
<tr>
<td></td>
<td>&gt; 4 myeloid gene mutations</td>
</tr>
</tbody>
</table>

## Lenalidomide

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Del</em>(5q)</td>
<td>PLT &lt; 280 x 10⁹/L</td>
</tr>
<tr>
<td><em>TP53</em> exon 4 R27P genotype</td>
<td><em>TP53</em> mutation</td>
</tr>
<tr>
<td></td>
<td>CRBN polymorphism A/A (rs1672753) + low <em>NPM1</em> expression in non-del(5q) patients</td>
</tr>
</tbody>
</table>
**Hypothesis**

- **MDS Patient**
- **Cytogenetics**
  - FISH
  - Targeted Gene Sequencing
- **Clinical Outcomes**
  - Efficacy
  - Safety
  - Survival
- **Treatment:**
  - HMA
  - Lenalidomide
- **Simulate Protein Network Disruptions**
- **Simulate Drug Interactions**
New Computational Biology Method

MDS Patient

Drug Interaction

Genomic Aberrations

60,000 Functional Interactions

Mathematical Modeling of Biology - Predictive Simulation Technology

Signaling, Metabolism & Epigenetics underlying cancer physiology
(i.e. Protein homeostasis, proteasome machinery, autophagy, oxidative stress, cell cycle machinery)

Published Literature of > 10,000 PubMed References

Protein Network Map
### 3 MDS Studies Investigated

<table>
<thead>
<tr>
<th>Study</th>
<th>LENALIDOMIDE</th>
<th>HMAs</th>
<th>LENALIDOMIDE + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>52 Patients</td>
<td>213 Patients</td>
<td>36 Patients</td>
</tr>
<tr>
<td>Disease</td>
<td>MDS del(5)q</td>
<td>MDS</td>
<td>MDS</td>
</tr>
<tr>
<td>IPSS Risk</td>
<td>Low-Intermediate</td>
<td>Intermediate-High</td>
<td>Intermediate-High</td>
</tr>
</tbody>
</table>
Lenalidomide

52 MDS patients with del(5q)
Treated with lenalidomide for a minimum of two months

2 patients without genomic information

4 patients without clinical outcome data

46 patients modeled

37 patients had achieved response in Mallo, et al.

9 patients did not achieve response in Mallo, et al.
Lenalidomide – Case #52 – Predicted Non-Responder
Lenalidomide

52 MDS patients with del(5q)
Treated with lenalidomide for a minimum of two months

- 2 patients without genomic information
- 4 patients without clinical outcome data

46 patients modeled

- 37 patients had achieved response in Mallo, et al.
  - 35 were correctly predicted
  - 2 were incorrectly predicted
- 9 patients did not achieve response in Mallo, et al.
  - 4 were correctly predicted
  - 5 were incorrectly predicted

<table>
<thead>
<tr>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>89%</td>
<td>44%</td>
<td>89%</td>
<td>80%</td>
<td>0.03586</td>
</tr>
</tbody>
</table>
## 3 MDS Studies Investigated

<table>
<thead>
<tr>
<th>Study</th>
<th>LENALIDOMIDE</th>
<th>HMAAs</th>
<th>LENALIDOMIDE + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>52 Patients</td>
<td>213 Patients</td>
<td>36 Patients</td>
</tr>
<tr>
<td>Disease</td>
<td>MDS del(5)q</td>
<td>MDS</td>
<td>MDS</td>
</tr>
<tr>
<td>IPSS Risk</td>
<td>Low-Intermediate</td>
<td>Intermediate-High</td>
<td>High Risk</td>
</tr>
</tbody>
</table>
HMA

213 higher risk MDS patients
Treated with azacitidine or decitabine (HMAs)

15 patients modeled
(randomly selected; all with abnormal karyotype)

7 patients had achieved response in Bejar, et al.

8 patients did not achieve response in Bejar, et al.
HMA – Case #203 – Predicted Responder

LOSS OF FUNCTION

AZACITIDINE

GAIN OF FUNCTION

ASXL1

EZH2

DNMT1

CpG

DUSP6

ERK

RAF

NRAS

AP1

CTNNB1

MYC

TP53

PROLIFERATION

SURVIVAL

APOPTOSIS

CCND1

CDKN1A/1B

CDKN2A/2D

MCL1

BCL2L1

BIRC5

BAX

BBC3

PMAIP1
213 higher risk MDS patients
Treated with azacitidine or decitabine (HMAs)

15 patients modeled
(randomly selected; all with abnormal karyotype)

7 patients had achieved response in Bejar, et al.
- 7 were correctly predicted
- 0 were incorrectly predicted

8 patients did not achieve response in Bejar, et al.
- 5 were correctly predicted
- 3 were incorrectly predicted

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>63%</td>
<td>100%</td>
<td>80%</td>
<td>0.02564</td>
</tr>
</tbody>
</table>
### 3 MDS Studies Investigated

<table>
<thead>
<tr>
<th></th>
<th>LENALIDOMIDE</th>
<th>HMAs</th>
<th>LENALIDOMIDE + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>52 Patients</td>
<td>213 Patients</td>
<td>36 Patients</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>MDS del(5)q</td>
<td>MDS</td>
<td>MDS</td>
</tr>
<tr>
<td><strong>IPSS Risk</strong></td>
<td>Low-Intermediate</td>
<td>Intermediate-High</td>
<td>High Risk</td>
</tr>
</tbody>
</table>
HMA + Lenalidomide

- **36 higher risk MDS patients**
  - Treated with a combination of azacitidine and lenalidomide for a median of 5 cycles

- **17 patients without genomic information**
- **10 patients studied**
  - Complete profiles
  - **8 patients had achieved response in Bejar, et al.**
  - **2 patients did not achieve response in Bejar, et al.**
- **9 patients with normal karyotype or wild type gene sequencing**
HMA+Len – Case # 1 – Predicted Responder

Diagram showing pathways for AZA, LEN, CDKN1A/1B, CDKN2A/2B, MCL1, BCL2L1, BIRC5, BAX, BBC3, PMAIP1, and TP53.
HMA + Lenalidomide

36 higher risk MDS patients
Treated with a combination of azacitidine and lenalidomide for a median of 5 cycles

17 patients without genomic information

10 patients studied
Complete profiles

8 patients had achieved response in Bejar, et al.
8 were correctly predicted

0 patients had not achieved response in Bejar, et al.
0 were correctly predicted

9 patients with normal karyotype or wild type gene sequencing

2 patients did not achieve response in Bejar, et al.
2 were correctly predicted

0 patients did not achieve response in Bejar, et al.
0 were correctly predicted

<table>
<thead>
<tr>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Summary & Plans

1. New simulation method to model MDS
   - Simulate cell proliferation rate, survival, and apoptosis
     + Multiple genomic mutations
     + Interacting genomic mutations
   - Create patient-specific map of disrupted protein network
   - Drug interactions within patient-specific network
2. Forecast drug sensitivity or resistance
3. Identify new biomarkers
   - Lenalidomide upregulation of beta-catenin paradoxically leading to drug resistance
   - GGH overexpression leading to HMA resistance

Plans
- Ongoing: prospective validation study, “iCare for Cancer Patients”
  - [https://clinicaltrials.gov/show/NCT02435550](https://clinicaltrials.gov/show/NCT02435550)
- Upcoming: randomized phase 2 study in relapsed/refractory MDS
  - Model-Informed Treatment versus Standard of Care
Acknowledgments

UF UNIVERSITY OF FLORIDA
- Christopher R. Cogle, M.D.
- Leylah Drusbosky, Ph.D.
- Regina Martuscello, Ph.D.
- Myron Chang, Ph.D.
- Fei Zou, Ph.D.

CELLWORKS
- Taher Abbasi
- Shireen Vali, Ph.D.

- Additional Support

LEUKEMIA & LYMPHOMA SOCIETY
fighting blood cancers

NIH National Institutes of Health
Research Training and Career Development