Precision Oncology: The Optimism and Pessimism from Keyboard to Bedside

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Disclosures

• I will discuss the off-label use of the following drugs:
  • Ruxolitinib
  • Imatinib
  • Bortezomib
  • Vorasidenib
• Member, Scientific Steering Committee, Celegene Connect MDS/AML Registry Study
• Founder, CancerPOP
Case Presentation

• 76 year-old white woman with profound fatigue. No recent infections.
• CBC: pancytopenia, requiring red blood cell transfusion
• Chemistry, Iron, B12, folate: normal
• Bone marrow: dysplastic hematopoiesis, 15% myeloblasts
• Cytogenetics: 46, X, del(X)(q23) → deletion of at least 42 known genes
• NGS: mutations in EZH2, IDH1, CUX1 and SRSF2
• Whole Exome Sequencing: hundreds of gene SNPs and gene copy number variations

• Treatment choices:
  ❑ Low intensity chemotherapy: Azacitidine or Decitabine
  ❑ High intensity chemotherapy: Cytarabine ± Anthracycline
  ❑ Allogeneic Hematopoietic Cell Transplant
  ❑ Palliative Care → Hospice
Elements of Precision Oncology

Treatment  Response
Elements of Precision Oncology

Mapping Disease Biology
Predicting Responses
Personalizing Treatment
Monitoring Response
Adapting Treatment
Single Gene, Single Drug Matching

GENE | DRUG
---|---
A | A
B | B
C | C

**SHIVA Clinical Trial, Lancet Oncology 2015**
refractory metastatic solid tumor, 10 gene-drug pairs

- Adverse events in molecularly targeted group

Graph showing progression-free survival:
- **Molecularly targeted agent**
- **Treatment at physician’s choice**

HR 0.88 (95% CI 0.65–1.19); p=0.41

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecularly targeted agent</td>
<td>99</td>
</tr>
<tr>
<td>Treatment at physician’s choice</td>
<td>95*</td>
</tr>
</tbody>
</table>
Varieties of Precision Oncology

In Vitro Drug Testing

Pros:
- Compact assay
- Complete intracellular programming
- Number of drug & combos
- Variety of read-outs possible
- Normal cell referencing
- Automation, high throughput
- Reproducible

Cons:
- Technical failure rate (historical)
- Correlates with clinical?
- Limited number of drugs
- Recommends same drugs given empirically
- Currently lacks cancer environment

In Vivo PDX testing

Pros:
- Includes environment

Cons:
- Correlates with clinical?
- Limited number of drugs
- Labor-intensive
- Technically challenging

Computational Modeling

Pros:
- Remotely accessible assay: mobile, cloud
- Multi-gene, multi-drug / high-dimensional
- Limitless number of drugs
- Immortalized model
- Network/pathway identification
- Updates with advancing knowledge
- Block-chain permissible

Cons:
- Correlates with clinical?
- Finite elements due to software coding
- Depends on data completeness
- Currently lacks cancer environment
Computational Biology Modeling & Digital Drug Simulation in MDS and AML

- Retrospective Studies

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.
5 were correctly predicted
3 were incorrectly predicted

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

Computational Biology Modeling & Digital Drug Simulation in MDS and AML

• Retrospective Studies

<table>
<thead>
<tr>
<th>Patient Cohort</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Modeled</td>
<td>46</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Patients Excluded</td>
<td>6</td>
<td>98</td>
<td>26</td>
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<tr>
<td><strong>MDS Risk Category</strong></td>
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<tr>
<td>Low: 48%</td>
<td>Low: 13%</td>
<td>Low: 0%</td>
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<tr>
<td>Int-1: 50%</td>
<td>Int-1: 27%</td>
<td>Int-1: 10%</td>
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<tr>
<td>Int-2: 2%</td>
<td>Int-2: 40%</td>
<td>Int-2: 50%</td>
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<tr>
<td>High: 0%</td>
<td>High: 20%</td>
<td>High: 40%</td>
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<tr>
<td><strong>Cytogenetic Abnormalities</strong></td>
<td>del(5q)+/- other abnormalities</td>
<td>Variety</td>
<td>Variety</td>
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<tr>
<td><strong>Treatment</strong></td>
<td>Lenalidomide 10 mg PO QD D1-21 every 28-day cycle</td>
<td>Azacitidine 75 mg/m2 SC QD D1-7 of each 28-day cycle or Decitabine 20mg/m2, IV QD D1-5 of each 28 day cycle</td>
<td>Azacitidine 75 mg/m2 SC QD D1-5 and Lenalidomide 10mg PO QD D1-21 of each 28-day cycle</td>
</tr>
<tr>
<td>Patients who Achieved Response (N, %)</td>
<td>37 (80%)</td>
<td>7 (46%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Patients Who Did Not Achieve Response (N, %)</td>
<td>9 (19%)</td>
<td>8 (53%)</td>
<td>2 (20%)</td>
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<tr>
<td>Correctly Predicted Responders (N)</td>
<td>33 (89%)</td>
<td>7 (100%)</td>
<td>8 (100%)</td>
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<tr>
<td>Correctly Predicted Non-Responders (N)</td>
<td>4 (44%)</td>
<td>5 (63%)</td>
<td>2 (100%)</td>
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<tr>
<td>Positive Predictive Value (%)</td>
<td>89%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Negative Predictive Value (%)</td>
<td>44%</td>
<td>63%</td>
<td>100%</td>
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</table>
Computational Biology Modeling & Digital Drug Simulation in MDS and AML

• Prospective Pilot Study

Comparative analysis
EMPIRIC vs CBM

- Sensitivity
- Specificity
- Positive Predictive Value
- Negative Predictive Value
- Accuracy
- Protein Network Validation

### Characteristic Participants Evaluable for Clinical Response, N = 50 (% patients)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median age (range)</th>
<th>Sex, n (%)</th>
<th>Disease and origin, n (%)</th>
<th>Diagnosis, n (%)</th>
<th>Prior therapy, n (%)</th>
<th>Cytogenetics, n (%)</th>
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<td>Male</td>
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<td>Sex, n (%)</td>
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<td>Disease and origin, n (%)</td>
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<td>MDS</td>
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<td>AML</td>
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<td>De novo</td>
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<td>Secondary</td>
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<td>CMML-2</td>
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<tr>
<td>Myelofibrosis</td>
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<td>Diagnosis, n (%)</td>
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<td>Newly diagnosed</td>
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<td>Relapsed/refractory</td>
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<td>Prior therapy, n (%)</td>
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<td>No</td>
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<td>Cytogenetics, n (%)</td>
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<td>Uninformative</td>
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<td>Complex</td>
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<tr>
<td>Other</td>
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Drusbosky, et al. *In review.*
Computational Biology Modeling & Digital Drug Simulation in MDS and AML

SENSITIVE

RESISTANT

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Correct prediction, n/N</th>
<th>Positive response prediction</th>
<th>Negative response prediction</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>P value</th>
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<td>HMA b</td>
<td>18</td>
<td>16/18</td>
<td>4</td>
<td>12</td>
<td>67%</td>
<td>100%</td>
<td>100%</td>
<td>86%</td>
<td>89%</td>
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<td>Lenalidomide</td>
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<td>2/2</td>
<td>2</td>
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<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Ruxolitinib</td>
<td>2</td>
<td>2/2</td>
<td>2</td>
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<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Imatinib</td>
<td>1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>1.000E-00</td>
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<tr>
<td>HI DAC c</td>
<td>17</td>
<td>17/17</td>
<td>14</td>
<td>3</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>3.615E-03</td>
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<td>Bortezomib</td>
<td>1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>1.000E-00</td>
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<tr>
<td>Cytarabine + fludarabine</td>
<td>1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>1.000E-00</td>
</tr>
<tr>
<td>Vorasidenib (AG-881)</td>
<td>1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>1.000E-00</td>
</tr>
<tr>
<td>7+3 d</td>
<td>18</td>
<td>14/18</td>
<td>12</td>
<td>3</td>
<td>92%</td>
<td>40%</td>
<td>80%</td>
<td>67%</td>
<td>78%</td>
<td>2.353E-01</td>
</tr>
<tr>
<td>Overall</td>
<td>61</td>
<td>55/61</td>
<td>33</td>
<td>3</td>
<td>94%</td>
<td>88%</td>
<td>94%</td>
<td>88%</td>
<td>90%</td>
<td>6.416E-05</td>
</tr>
</tbody>
</table>
Computational Biology Modeling & Digital Drug Simulation in MDS and AML

- Randomized, Phase 2 Clinical Trial

CLIA Lab
- Cytogenetics
- FISH
- WES
- CNV

Outcomes of Interest:
- Overall Response (CR+PR+SD+HI by IWG 2006)
- Transfusion Dependence
- Time to Relapse
- Time to AML
- Time to Death
- Mutant Allele Frequencies

FDA Approved Drugs

Treating Physician

CBM & DDS

Molecular Oncology Board

R

FDA IDE G170297

Relapsed/Refractory MDS Patients
Financial Times

High-profile health app under scrutiny after doctors’ complaints

Babylon advice service faces warnings it can miss symptoms of serious illness

STAT News

EXCLUSIVE

IBM’s Watson supercomputer recommended ‘unsafe and incorrect’ cancer treatments, internal documents show

By CASEY ROSS @caseymross and IKE SWETLITZ @ikeswetlitz / JULY 25, 2018
Synergy Among Precision Oncology

Ex-vivo sensitivity profiling to guide clinical decision making in acute myeloid leukemia: A pilot study


Leukemia Research, 2017
Physician – Patient Data Relationship
Physician – Patient Data Relationship

Visual Thinking Strategies
Find the Vowel

jklwkdvktz
bmnqifsdlt
klwrxjbjdsr
qnxvrjklpc
tkxbrtmds
klasdzwptr
fgstnbpctn
• What’s going on in this picture?

• What do you see that makes you say that?

• What more can you find?
Physician – Patient Data Relationship

Visual Thinking Strategies
Case Presentation

• 76 year-old white woman with profound fatigue. No recent infections.
• CBC: pancytopenia, requiring red blood cell transfusion
• Chemistry, Iron, B12, folate: normal
• Bone marrow: dysplastic hematopoiesis, 15% myeloblasts
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  ❏ High intensity chemotherapy: Cytarabine ± Anthracycline
  ❏ Allogeneic Hematopoietic Cell Transplant
  ❏ Palliative Care → Hospice
Physician – Patient Data Relationship

• Visual Training Exercises Among Radiologists
  • Adrian-Harris, *Radiography*, 1979
• Dolev, et al., *JAMA* 2001
• Naghshineh, et al., *J Gen Int Med*, 2008
• Commentary on Visual Thinking Practice
  • Braverman, *Clin Dermatol*, 2011
• Teaching Dermatology Residents to Observe More Closely
  • Huang, et al., *British Journal of Dermatology*, 2016