Molecular-Targeted and Immunotherapy of AML

Robert H. Collins, Jr., M.D.
Professor of Medicine
University of Texas Southwestern Medical Center
What’s the Biggest Advance in Adult AML Over the Last 40 years?
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A cynic who’s been around a long time:

“Zofran”

Current outcomes in AML > age 60
What’s the Biggest Advance in Adult AML Over the Last 40 years?

An alternative view:

“APL”
Case Report: APL 1988

• 24 year-old graduate student with fatigue and brusing

• Diagnosis: APL with t(15;17)

• Treatment:
  – 7 & 3 chemotherapy
  – FFP, platelets, cryoprecipitate

• Day 2 of treatment:
  – Intracranial hemorrhage and death
APL Genetics

- \( t(15;17) \)

- Late 1980s
  - Empiric treatment with all-trans retinoic acid \( \rightarrow \) remissions
  - Translocation cloned
    - Retinoic acid receptor alpha gene
    - PML gene
    - Fusion protein: PML-RARA
      - Science 1990;249:1577-80
Targeting the Molecular Defect in APML
Inducing Differentiation

ATRA

ATRA/chemo vs chemo

Optimized ATRA/chemo

NEJM 337:1021, 1997
Targeting the Molecular Defect in APML
All-trans Retinoic Acid and Differentiation
Arsenic Trioxide in APL

Zhang, XW et al. Science, 2010
Combined ATRA/Arsenic Trioxide Treatment of APL

A

<table>
<thead>
<tr>
<th>Months since Diagnosis</th>
<th>Probability of Event-free Survival</th>
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</thead>
<tbody>
<tr>
<td>0-12</td>
<td>1.00</td>
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<tr>
<td>13-24</td>
<td>0.90</td>
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<td>25-36</td>
<td>0.75</td>
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<tr>
<td>37-48</td>
<td>0.50</td>
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<td>49-60</td>
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No. at Risk

- ATRA–arsenic trioxide: 76, 73, 72, 28, 5
- ATRA–chemotherapy: 77, 68, 65, 27, 7

P = 0.02

B

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<thead>
<tr>
<th>Months since Diagnosis</th>
<th>Probability of Overall Survival</th>
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<tr>
<td>0-12</td>
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<tr>
<td>13-24</td>
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No. at Risk

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P = 0.02
Genetics ➔ Function ➔ Targeted Therapy

The lesson from APL: Mechanism-targeted therapy can be very effective
Genetics ➔ Function ➔ Targeted Therapy

FLT3
FLT3 in AML
Approximately 30% of cases, associated with poor prognosis


**FLT3 Inhibitors**
- Most target ITD mutation, resistance occurs through outgrowth of D835
- Crenolanib targets both ITD and D835 mutations
Case Report

AML Response to Crenolanib

- 35 year-old male
- AML with FLT3 ITD
- R/R disease

AC220

Crenolanib

Bridged to transplant
FLT3 Inhibitors that Target Both ITD and D835
Promising Early Results in R/R Patients

• Crenolanib:
  – Response rate 47% in R/R setting
  – Phase I/II studies of creno/chemo combos completed
  – Phase III studies about to start
  – Studies of post-creno relapse show that resistance is not mediated by FLT3 mutants

• Gilteritinib:
  – Similarly promising drug that targets both FLT3 ITD and TKD mutants

Collins R, ASCO 2014
Levis M, ASCO 2015
Genetics $\rightarrow$ Function $\rightarrow$ Targeted Therapy

IDH
Second Whole Cancer Genome Sequenced

- IDH1 (cytosolic) and IDH2 (mitochondrial)
- Krebs cycle enzymes
- Mutated in ~20% of AML cases
  - Also in MDS, MPN
- How do mutations in IDH cause cancer?
Mechanism of IDH mutated AML and Targeted with Specific Inhibitors
AG-120, AG-221

- Phase I-II study in R/R AML
- Response rate 40%
  - CR 20%
  - CRi/PR 18%
  - Stable 53%
- Median duration of response
  - 6 months
  - Some ongoing CRs
- Well-tolerated. Differentiation syndrome in many responders

Blood 122:2770, 2013
Blood, submitted
AG-221 for mIDH2 in AML

- 69 year-old man
- AML with 20% blasts
- Sent home on palliative care
- 2nd opinion
- Molecular testing → IDH2 mutation
- Ag-221 → CR in one month
- Transitioned to MUD-BMT with RIC. Remains in CR with minimal GVHD >1 year

- AG-221 and AG-120
  - Moving toward FDA approval
  - Being studied further in combination with chemo and other targeted agents in relapsed and up-front setting
Genetics $\rightarrow$ Function $\rightarrow$ Targeted Therapy

More Genes
Large-Scale Analysis of AML Genomes

NEJM 368:2059, 2013

NEJM 374:23, 2016
Organizing mutations into pathways

- Transcription factor fusions
- NPMc
- Tumor suppressors (TP53, WT1)
- DNA methylation (DNMT3A, IDH1, etc.)
- Activated signaling (Kinases, Ras, etc.)
- Myeloid transcription factors
- Epigenetic modifiers (Histone methylases, etc.)
- Cohesin complex genes
- Spliceosome complex genes

NEJM 368:2059, 2013
Using Molecular Data: Assessing Prognosis and Assigning Therapy

A

Gene Fusions

- inv(16)
- t(15;17)
- t(8;21)
- t(6;9)
- MLL fusions
- inv(3)

No Gene Fusions

- CEBPA
- IDH2
- NPM1
- Chromatin–spliceosome
- TP53–aneuploidy

B

- TP53 wt; not complex karyotype
- TP53 mut; not complex karyotype
- TP53 wt; complex karyotype
- TP53 mut; complex karyotype

C

- ASXL1 wt; SRSF2 wt
- ASXL1 mut; SRSF2 wt
- ASXL1 wt; SRSF2 mut
- ASXL1 mut; SRSF2 mut

NEJM 374:23, 2016
Using Molecular Data: Choosing Therapy with Current Targeted Drugs
Case Report: AML and Mast Cell Sarcoma

- 62 y.o. man with AML in remission for 3 years.
- CT → lytic lesion in pelvis
- Bx → mast cell sarcoma
- Very poor prognosis

- Is there any relationship between the AML and the mast cell sarcoma?
- Is there anything we can do to treat the mast cell sarcoma?
**Molecular Panels to Analyze Tumors and Guide Therapy**

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<tr>
<th>Gene</th>
<th>Gene Alteration</th>
<th>MAF</th>
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<tbody>
<tr>
<td>FLT3</td>
<td>S451F</td>
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<tr>
<td>IDH2</td>
<td>R140Q</td>
<td>42%</td>
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<tr>
<td>SRSF2</td>
<td>P95H</td>
<td>60%</td>
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**AML**

12-12

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<tr>
<th>Gene</th>
<th>Gene Alteration</th>
<th>MAF</th>
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</tr>
<tr>
<td>IDH2</td>
<td>R140Q</td>
<td>42%</td>
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<tr>
<td>SRSF2</td>
<td>P95H</td>
<td>38%</td>
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**Mast Cell**

5-15
Treatment Options

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient's tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
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<tbody>
<tr>
<td><strong>KIT</strong> Y503_F504insAY</td>
<td>Imatinib</td>
<td>Dasatinib</td>
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<tr>
<td></td>
<td></td>
<td>Everolimus</td>
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<tr>
<td></td>
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<td>Nilotinib</td>
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<td>Pazopanib</td>
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<td>Ponatinib</td>
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<td>Regorafenib</td>
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<td>Sorafenib</td>
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<td>Temsirolimus</td>
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<td>Sunitinib</td>
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<tr>
<td><strong>IDH2</strong> R140Q</td>
<td>None</td>
<td>Azacitidine</td>
<td>Yes, see clinical trials section</td>
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<tr>
<td></td>
<td></td>
<td>Decitabine</td>
<td></td>
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<tr>
<td><strong>SRSF2</strong> P95H</td>
<td>None</td>
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Treatment: Imatinib 400 mg/d. Local RT

Outcome:
Complete remission at 2 years

Potential future usefulness of IDH2 inhibitor?
Genetics ➔ Function ➔ Targeted Therapy

Compressing the Analysis
Combined Genetic and Functional Analysis to Define Targetable Molecular Drivers in Leukemia

• Chronic Neutrophilic Leukemia (CNL)
  – Elevated mature neutrophils
  – BCR/ABL, JAK negative
  – Progressive course, survival about 2 years
  – Pathogenesis unknown

• Genetic and functional analysis
  – Deep sequencing of tyrosine kinome
  – Functional drug and siRNA screening
    • Panels of kinase inhibitors
    • Panels of siRNA against all tyrosine kinases

CNL: CSF3R mutation that signals through JAK

NEJM 368:1781, 2013
Ruxolitinib in CSF3R-Driven CNL
Real-Time Functional Analysis to Choose Therapy for Refractory Leukemia

58 year-old man with refractory T-ALL

Blood 129:e26, 2017
R/R T-ALL—Response to Dasatinib

Upcoming Trial of This Approach in R/R AML/ALL

Blood 129:e26, 2017
Genetics ➔ Function ➔ Targeted Therapy

Compressing the Analysis

Large-Scale: The Beat AML Project
Beat AML 1.0: Finding and Treating New AML Targets

Large-scale analysis of 900 cases

OHSU        Illumina
UTSW        Intel
Stanford    AMP-Labs
Utah        Multip biotech/pharma

DNA & RNA sequencing
- DNA mutation
- RNA under or over expression
- Gene fusions

Functional analysis
- Systematic enzyme inhibition RNAi
- Inhibition of cell growth by drugs

Full genetic and functional workup

Integrated data analysis

Genetic Abnormalities
Leukemia Mechanism

Overarching Goal:
Patient-Specific Targeted Treatment
Functional Screening: IL-1 a Major Growth Factor for Leukemia

Blocking IL-1 inhibits AML growth

Providing IL-1 stimulates AML growth

Cell Reports 18:3204, 2017
IL-1 from *microenvironment* promotes AML growth through p38MAPK signaling
Beat AML 2.0 Clinical Study

Insights from many sources suggest new targeted therapies
Novel targeted agents include:
- IDH inhibitors
- CD33 antibodies
- AML checkpoint inhibitors
- Syk inhibitors

Upcoming trials for AML with mutated:
- FLT3
- IDH1
- NPM1
- p53

Patients with good responses may be transitioned to novel allogeneic SCT approaches utilizing engineered T cells.
Combining Molecular Targeted Therapy with Cellular Immunotherapy

[Image of a stem cell transplantation process]

[Graph showing % relapse for different conditions]

[Images of skin conditions and cellular immunotherapy cellular image]
Preventing GVHD With Post-Transplant Cyclophosphamide
Post-transplant cyclophosphamide
Baseboard for adoptive immunotherapy

BBMT, in press
Safety Switch-Gene Transduced T Cells

Safety-Switch in Donor Cells

$17 million CPRIT grant to develop this approach: Clinical studies led by UT Southwestern
Molecular-Targeted Therapy Followed by Engineered Stem Cell Transplant

- 63 year-old man
- Advanced refractory AML
- Molecular analysis $\rightarrow$ IDH1 mutation. Treated with AG-120 $\rightarrow$ CR
- Engineered allogeneic SCT from haploidentical son
  - CD34+ selected stem cells
  - T cells with suicide switch
- Alive and well at 1.5 years
Moving Forward in AML Treatment

Rapidly evolving approaches showing significant promise

- Molecular-targeted
- Novel cellular approaches

Current outcomes in AML > age 60

UTSW Referrals: 844-508-0265
Clonal Evolution of AML
(and thus heterogeneity of cell populations)
Clonal Evolution of AML
(and thus heterogeneity of cell populations)
Additional Mechanisms Under Study

- **DNA Methylation/Chromatin modification**
  - DNMT3A, 3B
  - DNMT1
  - TET1, TET2
  - IDH 1&2
  - MLL
  - NUP98
  - ASXL1
  - BCOR
  - EZH2
  - KDM6A

- **NPM1**

- **Tumor Suppressors**
  - TP53
  - WT1
  - PHF6

- **Cohesin complex**
  - SCC1
  - SCC3
  - SMC1
  - SMC1

- **Spliceosome mutations**
  - SF3B1
  - ZRSR2
  - SFRS2
  - U2AF1

- **Transcription factors**
  - PML/RARA
  - MYH11-CBFB
  - RUNX1-RUNX1T1
  - PICALM-MLLT10
  - CUX1
  - RUNX1
  - CEBPA

- **Activated Signaling**
  - FLT3
  - KIT
  - Other Tyr kinases
  - Ser-Thr kinases
  - KRAS/NRAS
  - PTPs

**Unifying Themes, Shared Pathways**
(targeting one may equal targeting several)