Future Targets for Acute Myeloid Leukemia

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Chair, Children’s Oncology Group Myeloid Disease Committee
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Acute Myeloid Leukemia

• Myeloid malignancies = 20% of childhood leukemias

• Three different major biological subtypes driving treatment stratification in AML
  • *PML-RARA* – Acute promyelocytic leukemia
  • Myeloid malignancies in Down syndrome
  • All others
Acute Promyelocytic Leukemia

**PML-RARA – t(15;17)**

N = PML (15q22)
    NPM (5q35)
    NuMA (11q13)
    PLZF (11q23)

N/RARα blocks promyelocyte differentiation
Leads to uncontrolled self-renewal

RARα (17q21)
Acute Promyelocytic Leukemia

*PML-RARA – t(15:17)*

Acute Promyelocytic Leukemia

*PML-RARA* – *t(15:17)*

![Graph showing survival rates for different treatment options.]

- **ATRA/ATO+chemo:** 91.7%
- **ATRA+chemo→ATO:** 78.6%
- **ATO:** 70-85% (87.6%, 3 y)
- **ATRA+chemo:** 60-80%
- **Chemo:** 35-45%

Pre-chemo
Acute Promyelocytic Leukemia

**PML-RARA – t(15:17)**

- ATRA/ATO+chemo: 91.7%
- ATRA+chemo→ATO: 78.6%
- ATO: 70-85% (87.6%, 3 y)
- ATRA+chemo: 60-80%

**Figure 1: Event Free Survival by Risk Grouping**

- Standard Risk (n=66)
- High Risk (n=35)

Kutny, et al, ASH 2015
AAML1331: A Phase III Study for Patients with Newly Diagnosed Acute Promyelocytic Leukemia (APL) using Arsenic Trioxide and All-Trans Retinoic Acid

**Induction:**

**Standard Risk Patients (WBC <10,000 at diagnosis)**
- Day: 1
- ATRA = All-trans retinoic acid
- ATO = Arsenic trioxide
- (further daily doses if not CR on Day 28 bone marrow)
- (Hydroxyurea and dexamethasone will be used to control leukocytosis if WBC rises to >10,000 during induction)

**High Risk Patients (WBC ≥10,000 at diagnosis)**
- Day: 1
- ATRA = All-trans retinoic acid
- ATO = Arsenic trioxide
- Dex = Dexamethasone
- Ida = Idarubicin
- (Ida = Idarubicin given on Days 1, 3, 5, 7)

**Consolidation:**

**Standard Risk and High Risk Patients**
- Week 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
- ATRA
- ATO
- RQ-PCR testing: ↑ ↑* (↑ Only if Week 14 RQ-PCR positive, repeat testing in 1-2 weeks)

**ATRA** = All-trans retinoic acid
**ATO** = Arsenic trioxide
AAML1331: A Phase III Study for Patients with Newly Diagnosed Acute Promyelocytic Leukemia (APL) using Arsenic Trioxide and All-Trans Retinoic Acid

- APL In a medical emergency
- Death in APL happens in the first couple weeks of therapy
  - Start ATRA early and often
  - Aggressive coagulopathy management

**Induction:**
- **Standard Risk Patients (WBC <10,000 at diagnosis)**
  - Day 1: ATRA (further daily doses if not CR on Day 28 bone marrow)
  - ATO (Hydroxyurea and dexamethasone will be used to control leukocytosis if WBC rises to >10,000 during induction)
- **High Risk Patients (WBC ≥10,000 at diagnosis)**
  - Day 1: ATRA (further daily doses if not CR on Day 28 bone marrow)
  - ATO
  - Dex
  - Ida
  - (Ida= Idarubicin given on Days 1, 3, 5, 7)

**Consolidation:**
- **Standard Risk and High-Risk Patients**
- **Week 1:**
  - ATRA
  - ATO
  - RQ-PCR testing:
    - Up
    - (*Only if Week 14 RQ-PCR positive, repeat testing in 1-2 weeks)

**TRA= All-trans retinoic acid**
**ATO= Arsenic trioxide**
**AAML1331: A Phase III Study for Patients with Newly Diagnosed Acute Promyelocytic Leukemia (APL) using Arsenic Trioxide and All-Trans Retinoic Acid**

<table>
<thead>
<tr>
<th></th>
<th>AAML0631</th>
<th>AAML1331</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic chemo</td>
<td>Yes - Mercaptopurine, cytarabine and 355mg/m² anthracyclines)</td>
<td>No</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>2 years</td>
<td>7-9 months</td>
</tr>
</tbody>
</table>

**PLZF-RARA excluded**
AML in Down Syndrome
AML in Down Syndrome – The Facts

• Children with Down Syndrome (DS) have a 10-20 fold higher incidence of leukemia.

• Children with DS less than 4 years have a 500-fold increased incidence of AML.

• Acute megakaryoblastic (AMKL) leukemia accounts for nearly half of all ML-DS.

• AMKL is rare in non-DS AML and is typically associated with t(1;22), a mutation not seen in ML-DS.
AML in Down Syndrome – The Facts

- Children with Down Syndrome (DS) have a 10-20 fold higher incidence of leukemia.
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- AMKL is rare in non-DS AML and is typically associated with t(1;22), a mutation not seen in ML-DS.
- In 2002, Wechsler et al. described in ML-DS mutations in GATA1, an essential transcription factor in hematopoiesis.
  - A stop codon results in a truncated but functional protein with a deficient or absent amino-terminal activation domain.
  - Mutations in GATA1 are found in nearly all patients with ML-DS diagnosed prior to age 4 years, but are rare in non-DS AML and in ML-DS in children older than 4 years.
AML in Down Syndrome – Leukemogenesis

Yoshida, et al.
AML in Down Syndrome – Leukemogenesis

Yoshida, et al.
AML in Down Syndrome – Leukemogenesis

Yoshida, et al.
AML in Down Syndrome – Leukemogenesis

Yoshida, et al.
AML in Down Syndrome – Leukemogenesis

- TMD and DS-AML are sequential phenotypes
- Concordant GATA1 mutation in same individual

Hitzler J 2005 Nat Rev Cancer
AML in Everybody Else
Study Entry

- **ADE + Aza**
  - **randomize**
  - **FLT3 ITD or mutation 17%**
    - **ADE + FLT3Inh**
    - **AE + FLT3Inh**
    - **MA + FLT3Inh**
  - **Ras Pathway mutation 33%**
    - **ADE + Ras/MEK Inh**
    - **AE + Ras/MEK Inh**
    - **MA + Ras/MEK Inh**
  - **No targetable abnormality or Methyltransferase mutation 44% (32% MT mutations)**
    - **ADE+ Aza**
    - **AE+ Aza**
    - **MA+ Aza**
  - **c-Kit 6%**
    - **ADE + c-Kit inh**
    - **AE + c-Kit inh**
    - **MA + c-Kit inh**

**BMT eligible – BMT then post BMT novel agent**
Progress in Childhood Leukemias

ALL

Hunger, Adamson, 2015

AML

Gamis, PBC, 2012
Progress in Childhood Leukemias

Childhood cancer survival

Proportion surviving after 2 years [%]

Year of Diagnosis


M. Hodgkin
Wilms Tumour
Acute lymphoblastic Leukemia
Non-Hodgkin Lymphoma
Ewing Sarcoma
Osteosarcoma
Rhabdomyosarcoma
Malignant Germ Cell Tumours
Neuroblastoma
Brain Tumours
Acute myeloid Leukemia

SEER

Nemours. Alfred I. duPont Hospital for Children
Progress in Childhood Leukemias

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SEER

7 + 3
Progress in Childhood Leukemias

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SEER

10 + 3
Progress in Childhood Leukemias

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Proportion surviving after 2 years [%]

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- M. Hodgkin
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- Ewing Sarcoma
- Osteosarcoma
- Rhabdomyosarcoma
- Malignant Germ Cell Tumours
- Neuroblastoma
- Brain Tumours
- Acute Tumours
- Acute myeloid Leukemia

3 + 10

SEER
Challenges for PM in AML – Cellular Diversity

Figure courtesy of the Seattle Cancer Care Alliance
Challenges for PM in AML – Cellular Diversity

[Diagram showing the cellular diversity in AML]

Figure courtesy of the Seattle Cancer Care Alliance
Challenges for PM in AML – Cellular Diversity

AML affects these.

And these.

And these.
Challenges for PM in AML – Cellular Diversity

DNA Meth, RNA seq, ATAC Assay

Figure courtesy of the Seattle Cancer Care Alliance
Challenges for PM in AML –
Mutational Diversity
Challenges for PM in AML – Mutational Diversity

Among cancers AML is one of the least mutated
But with great mutational diversity

126 of 721 pediatric validation cases had no recurrent mutation detectable at 600x.
PM in AML – Mutational Diversity

Leukemogenesis is leukemogenic
PM in AML – Mutational Diversity
Leukemogenesis is leukemogenic

- Ras mutations are common in t(8;21)
  - However…..
    - Only 79% present at diagnosis and relapse
    - 8% of patients gained mutations
    - 13% of patients lost mutations at relapse

Bachas, Blood, 2010
Challenges for PM in AML – Epigenetic Diversity

Figure 1: Transcriptional silencing of gene promoters via DNA methylation
Challenges for PM in AML – Epigenetic Diversity

Granulocyte-monocyte-like AML:
- Many normal karyotype
- M4
- M5
- Younger patients

Hematopoietic Stem Cell-like AML:
- Usually normal or complex karyotype
- MLL fusions.
- M0
- M1

DNA methylation signature: HSC-like vs. GMP-like

Courtesy of Tim Triche, Jr
PM in AML –
Leukemogenesis in AML

SEER statistics from 1999-2009
PM in AML –
Leukemogenesis in AML

- TMD and DS-AML are sequential phenotypes
- concordant GATA1 mutation in same individual

Hitzler J 2005 Nat Rev Cancer
PM in AML –
Leukemogenesis in AML

Young et al, Nature Comm, 2016 - Nurses Health Study (n=121,701)
• In serially banked peripheral blood samples from healthy 50-60 year old participants, 95% of individuals demonstrated clonal hematopoiesis, frequently involving $DNMT3A$ and $TET2$. 
Max Jan (STM 2012) mapped clonal evolution in NK-AML by computing variant allele frequencies (VAFs) in genotyped single-cell colonies.
Max Jan (STM 2012) mapped clonal evolution in NK-AML by computing variant allele frequencies (VAFs) in genotyped single-cell colonies.

TARGET vs. TCGA

Preleukemic mutations are rare or absent in pediatric AML

Pediatric patients often present with multiple proliferative mutations.
Divergent Epigenomes in Pediatric and Adult Acute Myeloid Leukemia Implicate Cell of Origin and Transcriptional Silencing of Immune Responses As Sources of Clinically Relevant Heterogeneity: A Report from the Children’s Oncology Group and NCI/COG Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative
**FLT3**

- Most common somatic mutations in childhood AML (20% of all AML), leading to autonomous activation of the intrinsic kinase domain

Leads to ligand independent activation of FLT3 receptors

Disrupts the auto-inhibitory function of the juxtamembrane domain region

Activation of tyrosine kinase of the FLT3

(Mechanism 1) ITD in exon 14 in the juxtamembrane domain region

(Mechanism 2) Point mutation in the activation loop of the kinase domain of FLT3

Pawar, 2014

Double blind placebo controlled trial of midostaurin in patients with FLT3 activating mutations
PM in AML –
Opportunities and Challenges

Opportunities
• Profound structural events suggest targetability
• Altering the epigenome may impact function of a mutation

Challenges
• Clonal evolution
• Few drugs for relevant targets
• Introducing new drugs on a maximally toxic backbone
Final Results of a Phase III Randomized Trial of VYXEOS™ (CPX-351) Versus 7+3 in Older Patients With Newly Diagnosed High-Risk (Secondary) AML


June 2016
CPX-351

Background

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
CPX-351

Background

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
CPX-351

Background

- A Phase 3 presented at ASCO2016 compared CPX351 to 7+3

<table>
<thead>
<tr>
<th>CPX351</th>
<th>7+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>100U/m² CPX351 days 1, 3, 5 (44mg/m² Dauno)</td>
<td>Dauno 60mg/m² x 3d, AraC 100mg/m² x 7d</td>
</tr>
<tr>
<td>100U/m² CPX351 days 1, 3 (44mg/m² Dauno)</td>
<td>Dauno 60mg/m² x 2d, AraC 100mg/m² x 5d</td>
</tr>
<tr>
<td>65U/m² CPX351 days 1, 3, 5 (29mg/m² Dauno)</td>
<td>Dauno 60mg/m² x 2d, AraC 100mg/m² x 5d</td>
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</table>
CPX-351

Background

Odds Ratio (95% Conf. Int.)

CR

- CPX-351 (n=153)
- 7+3 (n=156)

- CR: 37.3 (1.69, 2.78)
- CR + CRi: 47.7 (1.77, 2.81)

Note: Percentages reflect number with endpoint out of column total. Odds ratios are calculated with the 7+3 arm as the reference group. P-value is from a comparison of rates between treatment arms and is based on the Mantel-Haenszel test stratifying by age and AML type.
Response Rates of FLT3, NPM1, and CEBPα Mutated Patients

**CR + CRi RATE**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>CPX-351 ( n=22 )</th>
<th>7 + 3 ( n=20 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3 mutated</td>
<td>68.2/92.3 ( n=13 )</td>
<td>58.3/25.0 ( n=12 )</td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td>15/22</td>
<td>3/13</td>
</tr>
<tr>
<td>FLT3-TKD</td>
<td>12/19</td>
<td>2/7</td>
</tr>
<tr>
<td>CEBPα</td>
<td>33.3/20.0 ( n=5 )</td>
<td></td>
</tr>
</tbody>
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**Response Rate (responders/number of patients)**

- **CPX-351**
  - FLT3 mutated: 15/22
  - FLT3-ITD: 12/19
  - FLT3-TKD: 3/3
- **7 + 3**
  - FLT3 mutated: 5/20
  - FLT3-ITD: 3/13
  - FLT3-TKD: 2/7
Overall Survival of FLT3 Mutated Patients

KAPLAN-MEIER CURVE FOR OVERALL SURVIVAL BY ARM

BASELINE FLT3 POSITIVE SUBJECTS RECEIVING AT LEAST 1 DOSE OF STUDY DRUG

**CPX-351**

- 7 + 3
- Events/N: 17/22
- Median Surv. (95% CI): 10.25 (5.62, 14.95)

**7 + 3**

- Events/N: 18/20
- Median Surv. (95% CI): 4.55 (1.45, 10.32)

Hazard ratio = 0.57 (0.24, 1.33)

*p*-value = 0.093

Medeiros, 2015 – Unpublished Data
CD33 Targeting with GO

Gamis et al, JCO, 2014

Pollard, ASH, 2015

Tarlock et al, CCR, 2015
CD33 Targeting with GO

Gamis et al, JCO, 2014

Pollard, JCO, 2016
Study Entry

CPX-351 + GO

randomize

DA + GO

FLT3 ITD or mutation 20%

ADE + FLT3Inh

AE + FLT3Inh

MA + FLT3Inh

BMT eligible – BMT then post BMT novel agent
Precision Medicine in AML

• **The Promises**
  - Improved survival
  - Reduced Side effects

• **The Challenges**
  - Varying degrees of oncogene addiction
  - The role of multiple oncogenic hits.
  - Increasingly small molecular subsets of AML
  - Shifting oncogene expression
  - Diagnostic sequencing

• **The Future**
  - Broadly targeted therapies (ADC, cell-based therapies)
  - Small molecule inhibitors in the setting of oncogene addiction
  - Develop diagnostic and monitoring assays and leukemogenic modeling
  - Targeted strategies as well as targeted therapies

Nemours. Alfred I. duPont Hospital for Children
Thank You

The COG Myeloid Disease Committee

- Todd Alonzo
- Alan Gamis
- Lillian Sung
- Matthew Kutny
- John Gregory
- Johan Hitzler
- Jason Berman
- Todd Cooper
- Richard Aplenc
- Jessica Pollard
- Soheil Meshinchi
- Bob Arceci