Subset Specific Therapy in High Risk Myeloid Malignancies. Are We Making Progress?

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The University of Chicago
Disclosure Information
23rd Annual Developmental Therapeutics Symposium
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• I have the following financial relationships to disclose:

Consultant for: CTI/Baxalta, Dava Oncology, Pfizer and Jazz Pharmaceuticals
Grant/Research support from: AbbVie, Agios, Astex, Celgene, CTI/Baxalta, NS-Pharma, Janssen and Incyte
Honoraria from: AbbVie
Membership on Board or Advisory Committee: ABIM

• I will discuss the following investigational use in my presentation: FLT3 Inhibitors, IDH1/2 Inhibitors, BCL2 Inhibitors, CPX-351, MEK Inhibitors
Objectives

- Review new developments and agents recently approved for specific subsets of acute myeloid leukemia
- Highlight significant ongoing areas of unmet need in high risk myeloid neoplasms
- Review upcoming novel approaches for high risk genotypic subsets
High Risk Myeloid Malignancies

Acute Myeloid Leukemia
Poor risk molecular or cytogenetic features
Relapsed refractory

Myelodysplastic syndromes
Higher risk disease

Myeloproliferative neoplasms
Advanced Myelofibrosis

Propensity to evolve to AML
Survival of 1124 adults with newly diagnosed AML according to cytogenetic risk group

Favorable risk (n=190; median=7.6)
Intermediate risk (n=686; median=1.3)
Adverse risk (n=248; median=0.5)
AML is molecularly heterogeneous

Dohner et al, Blood 2017
Selected Landmarks in AML

- 7+3 associated with high CR rates
- Idarubicin approved for AML
- Gemtuzumab ozogamicin for AML>60y/o in relapse
- Gemtuzumab ozogamicin withdrawn from the market
- Next Gen Sequencing
- Focus on subset specific therapy

- 1973: Cytogenetic risk stratification
- 1990: Idarubicin approved for AML
- 2000: Gemtuzumab ozogamicin for AML>60y/o in relapse
- 2010: Gemtuzumab ozogamicin withdrawn from the market
- 2017: 4 new FDA approvals: Midostaurin, Enasidenib, CPX-351, Gemtuzumab ozogamicin
FLT3 Receptor and Activating Mutations

Mutations cause ligand independent dimerization and constitutive activation
Occur later in leukemogenesis
Clinical phenotype: high WBC, poor prognosis
OS at 5 yrs=10% for FLT3ITD, NPM1 wt

Midostaurin (Rydapt) for Newly Diagnosed FLT3-mutated AML < 60 years  CALGB 10603 / RATIFY
Screened n=3277 enrolled n=717

STRATIFICATION:
TKD; ITD with allelic ratio <0.7 ‘vs’ ≥0.7

- Midostaurin approved by FDA for newly diagnosed adult AML at dose of 50 mg bid on days 8-21 of each cycle of induction and consolidation chemotherapy
- Median OS (mo): Midostaurin 74.7 (31.7-NE); placebo 25.6 (18.6-42.9)
- Allogeneic stem cell transplantation rate 57%

Hazard Ratio*: 0.77
1-sided log-rank p-value*: 0.0074

Challenges associated with development of FLT3 inhibitors to date

- Suboptimal PK/PD properties
  - Lack of reliable and sustained FLT3 kinase inhibition
- Emergence of resistance mechanisms
  - FLT3 point (TKD) mutations
  - Other pathways that may provide “escape” from FLT3 inhibition e.g MEK pathway
- Significant clonal heterogeneity
  - Multiple other gene mutations may occur even within the FLT3 mutant clone in individual patients

Odenike O et al, Seminars in Oncology 2011, 38: 196-214
FLT3 inhibition in AML, what’s next?

- More potent inhibitors in both the frontline setting and relapsed refractory setting with optimized PK/PD properties - gilteritinib, crenolanib
  - Role in changing natural history will reside in determining optimal combination with chemotherapy or azanucleosides
- Role in maintenance post allogeneic stem cell transplant?
Survival of 1124 adults with newly diagnosed AML according to cytogenetic risk group

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CPX-351 (Vyxeos): an old combination packaged in a new formulation

- Approved for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
- 100-nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
First-line CPX-351 in High-Risk AML

Figure. Landmark Survival Analysis at Time of Transplant

- **CPX-351 7+3**
  - Events / N: 18/52
  - Median Surv. (95% CI): Not Reached (10.25, 6.21, 16.69)
  - Log-rank p-value: 0.0046

- **7+3**
  - Events / N: 26/39
  - Median Surv. (95% CI): 5.95 (4.99, 7.75)
  - HR: 0.69, P = 0.005
The way forward with CPX-351?

- Ongoing discussion re: moving this into the frontline investigation in HR-MDS. Inducing deeper responses at the outset and consolidating with azanucleosides/transplant
- May be worthy of investigation in MPN-blast phase
- Will this agent given tolerability lend itself to combination with novel targeted biologics?
Targeting mutant IDH1/2

- **Mutations in IDH1/2**
  - Lead to elevated 2HG and inhibition of αKG enzymes and epigenetic dysregulation
  - Occur in 20% of AML; also MDS/AML, MPN-BP

- **IDH1/2 inhibitors active in IDH mutant AML**
  - Enasidenib approved for R/R IDH2 mutant AML
  - ORR-40% (19% CR)
  - DOR=5.8 months
  - OS=9.3 months

Adapted from: Gagne et al, Trends in Cell Biology, 27; 738-52

1. Dinardo CD, Leukemia, 2016; 30: 980
2. Stein EM, Blood 2017 E-pub
3. Stein EM, Blood, 2016, ASH annual meeting abstracts # 343
Maximizing the potential of IDH inhibitors

- Combination therapies with azanucleosides (unfit patients/poor molecular characteristics), or chemotherapy (fit patients) or novel therapeutics e.g. BCL2 inhibitors

- Identifying other molecular subsets (with elevated 2-HG, no obvious mutation) who may benefit
# AML biology predicts response to cytarabine + anthracycline chemotherapy

<table>
<thead>
<tr>
<th>Risk status</th>
<th>Cytogenetics</th>
<th>Molecular abnormalities</th>
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</thead>
<tbody>
<tr>
<td>Better risk</td>
<td>inv(16) or t(16;16) or t(8;21) without c-KIT mutation, t(15;17)</td>
<td>Normal karyotype with <strong>NPM-1 mutation</strong> in the absence of <strong>FLT-3 ITD</strong> or isolated biallelic <strong>CEBPα</strong></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Normal karyotype Trisomy 8 alone t(9;11) Other not defined</td>
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<td>Poor risk</td>
<td>Complex (≥3 clonal abnl) Monosomal karyotype -5, 5q-, -7, 7q-11q23 (not t(9;11)) Inv(3), t(3;3) t(6;9), t(9;22)</td>
<td>Normal karyotype with <strong>FLT-3 ITD</strong> mutation  <strong>TP53 mutation</strong></td>
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TP53 mutant AML is chemoresistant

Intensive chemotherapy

![Graph showing survival rates with TP53 altered and TP53 unaltered, marked "P < .0001"]

Rucker, Blood 2012

10 day decitabine

![Graph showing survival rates for TP53 wild-type and TP53 mutant, marked "P = 0.79"]

No. at Risk
- TP53 mutation: 21, 20, 7, 4, 2
- Wild-type TP53: 78, 51, 31, 16, 7

Welch, NEJM 2016
BCL2 inhibition in myeloid neoplasia

- Venetoclax is a potent orally bioavailable inhibitor of BCL2
- Preclinical evidence of synergy with hypomethylating agents
- Phase 1b, trial of venetoclax in combination with DEC or AZA in older (≥65 years) treatment-naive patients with AML (NCT02203773); ORR-61%.
- Randomized trials ongoing in AML
- Combination trials ongoing in HR-MDS (treatment naïve and HMA failure-NCT02942290; NCT02966782).

Konopleva Cancer Discovery, 2016; 6:1106
Bogenberger JM, Leukemia 2014; 28:1657
Tsao T, Annals Hematology 2012; 91:1861
Dinardo C, Lancet Oncol 2018
Decitabine/venetoclax in high risk AML
U of C: PCCC trial

- Based on preclinical evidence of synergy and activity of both drugs in TP53 mutant malignancies

- Inclusion criteria
  - TP53 mutant and/or poor risk karyotype
  - Agnostic to age and will include secondary AML (MPN-BP, MDS-AML, t-AML)

<table>
<thead>
<tr>
<th>Drug</th>
<th>D1-10</th>
<th>D10-14</th>
<th>D15-21</th>
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<tbody>
<tr>
<td>Decitabine</td>
<td>X</td>
<td></td>
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<tr>
<td>venetoclax</td>
<td>X</td>
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Molecular Pathways & Targets in Myeloid Neoplasms

Proliferation and survival

- JAK2
- MPL
- RAS
- FLT3
- cKIT
- CBL
- PTPN11

Epigenetic deregulation

- RUNX1
- ASXL1
- WT1
- TET2
- IDH1/2
- EZH2
- DNMT3A
- CUX1

Kinase inhibitors

Epigenetic modulators

Malignant myeloid transformation
Combined DNMT inhibition and MEK inhibition in high risk myeloid neoplasia IRB#0774

- Based on preclinical evidence of synergy\(^1\), and our clinical experience with single agent selumetinib in AML\(^2\)

- **Inclusion criteria**
  - Higher-risk MDS, MPN, MDS/MPN overlap syndromes including CMML
  - Disease characterized by mutation known to result in RAS pathway activation (includes JAK2 mutant MPN)

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<tr>
<th>Drug</th>
<th>D1-7</th>
<th>D8-14</th>
<th>D15-21</th>
<th>D22-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine 75mg/m2/d</td>
<td>X</td>
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<tr>
<td>MEK inhibitor Selumetinib</td>
<td></td>
<td>X</td>
<td>X</td>
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<td>escalating doses</td>
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Wu et al, Cell Reports 2014 \(^1\)
Jain N...Odenike, Clinical Cancer Research 2014 \(^2\)
### Institutional OncoPlus GMP Cancer Panel

**Institutional OncoPlus GMP Cancer Panel**

<table>
<thead>
<tr>
<th>Genes</th>
<th>Description</th>
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| \( \geq 1000 \) total genes | - 316 genes in Tier 1 (Higher clinical relevance, higher probe concentration, higher depth)  
- 896 genes in Tier 2 (Research-related content)  
- 16 genes for fusions (including ALK, RET and ROS1 for lung cancer)  
- BK, JC, HPV 16/18, HHV4, HHV8, HTLV-1 |
| Clinically reported genes ~150 |  
Accepted specimens – FFPE, blood, bone marrow and fine needle aspirates |

**Institutional OncoPlus GMP Cancer Panel**

**Courtesy of Jeremy Segal, GMP Division, University of Chicago**
Novel Pathways under investigation in myeloid malignancies

- T Cell
- Immune Checkpoint Inhibition
  - TCR
  - PD-1
  - CTLA-4
- IDH Inhibition
- BCL2 inhibition

- Splicing Modulation
- Splice Mut

- Kinase Inhibition
  - RAS
  - P13K
  - AKT
  - mTOR
  - RAF
  - MEK
  - ERK

- HMA
- HDACi
- BETi
- LSD1i

Adapted from Odenike O, Hematology, 2017
Looking to the future…

- Subset specific therapy is here to stay
  - in AML
    - Midostaurin, enasidenib, gemtuzumab ozogamicin, CPX-351
    - Relative magnitude on natural history is modest

- In MDS and high risk MPNs
  - 90% harbor gene mutations
  - efforts need to be made in the context of ongoing trials to identify subsets that may benefit from specific approaches

- Accelerating clinical trial development by conducting focused early phase trials, and moving tolerable combinations more rapidly into the frontline setting.
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  - Kristen Pettit

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  - Supriya Perambakan
  - Mary Sherrell

- Statisticians
  - Theodore Karrison
The End!
First-line CPX-351 in High-Risk AML

Figure. Landmark Survival Analysis at Time of Transplant

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