Algorithms for AML

29th Annual Fall Cancer Conference
West Virginia University

Cleveland Clinic

@MattKalaycioMD
Objectives

1) Describe newer treatments for AML
2) Outline the latest approaches to the management of AML
3) Finish on time
4) Make friends
Conflict of Interest Disclosure
Newly diagnosed AML

- **“Fit” and < 80 years**
  - Clinical Trial
  - If ineligible or no trials available:
    - FLT3-ITD+ or TKD+
      - Age < 60 years (7+3 M)
        - IDA12 + Ara-C 100 + M
      - Age ≥ 60 years (7+3 M)
        - D60 + Ara-C 100 + M
    - FLT3-ITD- and TKD-
      - Age < 60 years (7+3)
        - IDA12 or D90 + Ara-C 100
      - Age ≥ 60 years (7+3)
        - D60 + Ara-C 100
    - day 14-17 bone marrow biopsy
    - (+) CPX-351
    - (-) CR
    - CRi
    - Post-remission (Risk-based) strategy
  - sAML
  - GO + 7 + 3 for fav/Int risk AML
  - Refractory Disease
    - Clinical Trial
    - If ineligible or no trials + good PS
      - Allo-HCT (if transplant eligible and donor available)
    - CRi

- **“Unfit” or > 80 years**
  - Clinical Trial
  - If ineligible or no trials:
    - DNMTi (AZA, DAC)
      - LDAC
      - Int/Poor risk AML - Venetoclax
      - Fav/Int risk AML - Gemtuzumab Ozogamicin (GO)
    - Refractory disease or Progressive disease
      - DNMTi (AZA, DAC) /LDAC if not used before
        - FLT3+ AML - AZA + sorafenib
        - FLT3 inhibitors monotherapy
        - IDH-1/2 inhibitors
        - Venetoclax + HMA (or LDAC) if VEN not used before
      - GO if not used before
      - Refractory disease or Progressive disease
      - GO + 7 + 3 for fav/Int risk AML
      - CRi

Metaphase Cytogenetics
(Molecular analysis –Next generation sequencing) / FLT3 gene mutation analysis
Tissue Banking / Research Sample (IRB 5024)
HLA typing

- Post-remission (Risk-based) strategy
- CR
- CRi
- Refractory Disease
- Clinical Trial
- If ineligible or no trials + good PS
  - Allo-HCT (if transplant eligible and donor available)
Age <60

Healthy

7+3

Supportive Care
Antifungals
Platelets
Growth factors

Consolidation

Cytogenetics
- t(8;21)
- Inv16
- t(9;11)

Molecular
- CEBP1a
- NPM1

HDAC x 4

AlloBMT

Cytogenetics
- -7, -5, inv3
- -11q23, +11
- Complex

Molecular
- TP53
- ASXL1
- FLT3

DNR 90mg/m²
D14 BMBx
Repeat if +
Gemtuzumab Ozogamicin

Hitzler & Estey. Haematologica 104: 7, 2019
Gemtuzumab Ozogamicin
Gemtuzumab Ozogamicin

- GO is a new standard of care for patients with favorable cytogenetics
- Less so for those with intermediate CG
- Do not use in those headed to BMT
FLT3 Inhibitors

Daver et al, Leukemia 33: 299, 2019
• 717 pts randomized before treatment
• 7+3 (60mg/m²)
• Midostaurin or placebo 50 mg orally bid D8-21 for induction, consolidation, and maintenance x 1yr
• BMT OK
FLT3-ITD+ AML
Perl et al, Lancet Oncol 18: 1061, 2017

• 252 pts Phase 1-2
• Gilteritinib once daily
• Very active with GI and hepatic toxicity

In R/R FLT3+ AML, Phase 3 ADMIRAL trial showed Gilt improved 1y OS from 17% with chemo to 37% (95% CI, 31-44%).
Perl et al, AACR 2019
FLT3-ITD+ AML

• Midostaurin is new standard of care for newly diagnosed patients

• Gilteritinib is new standard of care for relapsed/refractory patients
  - What about those pts previously treated with midostaurin?

• BMT still indicated
  - Maintenance?
Indications for BMT

- Primary refractory
- sAML and tAML
- High-risk
  - Cytogenetics
  - Molecular
    - FLT3 ITD
    - TP53

Brunet et al, JCO 30: 735, 2012
AML in Younger Patients

- Algorithm fails
  - Borderline cases
  - Fertility issues
  - Patient preference
- Goal remains cure
- Not much has changed
  - GO
  - FLT3+

Bower et al, Blood Ca J 6:e390, 2016
Treating Older Patients

- Low-dose AraC bid improves OS vs BSC
- Neither 5AZA nor Decitabine have been compared to LDAC with bid schedule
  - No FDA approval, but OK by NCCN
- LDAC is the standard of care?
LDAC

Burnett AK et al, Cancer 109: 1114, 2007
Trying to improve on LDAC

Table 1. Outcome of Low-dose Ara-C Over Time Compared With Other Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparator, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BSC</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>1y</td>
<td>24</td>
</tr>
<tr>
<td>2y</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2. Pick a Winner Trial Options

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Era</th>
<th>Stage 1 Success</th>
<th>Phase III Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDAC + tipifarnib</td>
<td>2006-2008</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>LDAC + ATO</td>
<td>2007-2009</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>LDAC + GO</td>
<td>2006-2010</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>2006-2010</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sapacitabine</td>
<td>2010-2012</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>LDAC + quizartinib</td>
<td>2012</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vosaroxin</td>
<td>2012-2013</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>LDAC + Vosaroxin</td>
<td>2012-2013</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>LDAC + ganetespib</td>
<td>2012-2014</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>LDAC + tosedostat</td>
<td>2014-2017</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Burnett AK, Clin Lymphoma Myeloma & Leuk 18:553, 2018
- AML Age >65
- AZA vs CCR (BSC, LDAC, or IC)

- RAEB Blasts >10%
- AZA vs CCR
Hedgehog Signaling Pathway
Pasca de Magliano et al, Nat Rev Cancer 3: 903, 2004
Glasdegib
Cortes et al, Leukemia 33: 379, 2019

- Age >55 with AML or RAEB >10% blasts
- Unsuitable for induction
  - Age >75, Creat >1.3, LVEF < 45%
- Randomized 2:1 to LDAC +/- Glasdegib
  - LDAC 20mg sq bid for 10 days
  - Glasdegib 100mg once daily
Glasdegib/LDAC vs Azacytidine

Fig 2: Kaplan-Meier estimate of overall survival, full analysis set. CI: confidence interval, HR: hazard ratio, LDAC: low-dose cytarabine, OS: overall survival.
Venetoclax

Under BCL2 overexpression cancer cells evade apoptosis by sequestering proapoptotic proteins

Venetoclax selectively binds to BCL2 and liberates proapoptotic proteins that initiate apoptosis

Figure 1 Many cancer cells are able to evade apoptosis through impairment of the mitochondrial apoptotic pathway, controlled by proapoptotic (eg. BAK, BAX, BIM) and prosurvival (eg. BCL2, BCL-X) members of the BCL2 family.

Notes: In CLL, cells show BCL2 overexpression. The BCL2 inhibitor venetoclax selectively binds to BCL2 and liberates proapoptotic proteins, inducing mitochondrial outer-membrane permeabilization and leading to caspase activation. This reaction induces apoptosis.

Abbreviation: CLL, chronic lymphocytic leukemia.

Huber et al, Oncotargets and Therapy 10:645, 2017
LDAC+ Venetoclax
Wei et al, JCO prepublished, 2019

• Venetoclax began at 50 or 100 mg and increased over 4 to 5 days to the target venetoclax dose; dosing was continued through day 28 of each cycle.
• Age >60, secondary AML, unfit for induction, WBC <25, no CBF
• No DLT or TLS, 600mg daily was target dose
• CR 26%, CR/Cri 54%, DOR 8.1m
Ramp up dosing starting D1 in hospital
  - Target doses of 400 (n=60), 800 (n=74), or 1200mg (n=11) daily

Age >65, secondary AML, unfit for induction, WBC <25, no CBF

No DLT or TLS, but more AE at 1200mg daily
  - Febrile neutropenia in 32%
HMA + Venetoclax
DiNardo et al, Blood 133: 7, 2019

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>CR + CRi</th>
<th>Med DOR</th>
<th>Med OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDAC + V600</td>
<td>82</td>
<td>54%</td>
<td>8.1m</td>
<td>10.1m</td>
</tr>
<tr>
<td>HMA + V400</td>
<td>60</td>
<td>73%</td>
<td>12.5m</td>
<td>NR</td>
</tr>
<tr>
<td>HMA + V800</td>
<td>74</td>
<td>65%</td>
<td>11m</td>
<td>17.5m</td>
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21 patients proceeded to stem cell transplant

No difference in CR by age, cytogenetics, or secondary AML

CR = 71% in 35 with IDH1/2 mutations

CR = 47% in 36 with TP53 mutations and 5.6m DOR
HMA + Venetoclax
DiNardo et al, Blood 133: 7, 2019

Figure 2. Overall survival by venetoclax dose levels (dose escalation + dose expansion cohorts)
HMA + Venetoclax

• In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
  • This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

• Comorbidities that preclude the use of intensive induction chemotherapy?
Age >60

7+3

GO if CBF & CD33+
Midostaurin if FLT3+

Consolidation

IDAC x 4

Inv16

Cytogenetics

AlloBMT

Select Pts

Molecular

CEBP1a
NPM1

Very Select Pts

Targeted Therapy

CPX-351


Huls et al, Blood 133:1457, 2019

5Aza or Decitabine + Venetoclax

Maintenance

5AZA x 1y

Relapse

AlloBMT

Less fit

-7 TP53

Simplified

Madanat, Kalaycio, and Nazha; ACTA Medica Academica, In press, 2019
HMA for Relapsed/Refractory AML

Stahl et al, Blood Adv 2: 923, 2018

[Graph showing survival probability over time in months]
Identifying AML Targets
Gu et al, J Clin Invest 128: 4260, 2018
IDH Mutations
IDH inhibitors

Enasidenib
Stein et al, Blood 130:722, 2017

Ivosidenib
DiNardo et al, NEJM 378:2386, 2018
IDH inhibitors as initial therapy

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IVO V+HMA

27 71%

PFS 75% 12m

Burnett AK, Clin Lymphoma Myeloma & Leuk 18:553, 2018

Roboz et al, ASH 2018, Abs 561
DiNardo et al, Blood 133: 7, 2019
Gilteritinib for FLT3+ R/R AML
Perl et al, Lancet Oncol 18:1061, 2017
<table>
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<th>Gene</th>
<th>Frequency</th>
<th>Impact on prognosis</th>
<th>Comments</th>
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<tbody>
<tr>
<td>FLT3</td>
<td>20-25% (ITD) and 5-10% (D835 TKD)</td>
<td>Inferior survival for ITD mutations and prognostic significance of D835 TKD mutations unclear</td>
<td>More common in NK acute myeloid leukaemia (&lt;35% for ITD mutations), FLT3-ITD mutation with high allelic burden (ie, ≥1.0) associated with worse prognosis than lower allelic burden, prognosis affected by concomitant NPM1 mutation status, and prognostic significance not fully established with widespread use of FLT3 inhibitors</td>
</tr>
<tr>
<td>NPM1</td>
<td>About 30%</td>
<td>Superior survival in the absence of high allelic burden. FLT3-ITD mutation</td>
<td>More common in NK acute myeloid leukaemia (&lt;60%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in younger patients, coexisting chromosomal abnormalities do not affect prognosis, substantial association with concomitant FLT3, IDH1/2, and DNMT3A mutations, and can be used to monitor for minimal residual disease</td>
</tr>
<tr>
<td>CEBPA</td>
<td>About 10%</td>
<td>Superior survival (only if biallelic)</td>
<td>More common in NK acute myeloid leukaemia (&lt;20%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in younger patients, coexisting chromosomal abnormalities do not affect prognosis, and germline mutations with familial predisposition to acute myeloid leukaemia have been described</td>
</tr>
<tr>
<td>KIT</td>
<td>About 10%</td>
<td>Inferior survival in CBF acute myeloid leukaemia</td>
<td>More common in CBF acute myeloid leukaemia (present in 25-35%) than in non-CBF, poor prognosis more notable in acute myeloid leukaemia with t(8;21) than with inv(16). KIT inhibitors (e.g., dasatinib) are being evaluated in clinical trials of CBF acute myeloid leukaemia</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>About 20%</td>
<td>Conflicting reports on impact on survival</td>
<td>More common in NK acute myeloid leukaemia (&lt;35%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in older adults, CHIP mutation, inferior prognosis particularly when present with other mutations (e.g., IDH2&lt;sup&gt;wt&lt;/sup&gt;), and is associated with concomitant NPM1 mutations, IDH1 and IDH2&lt;sup&gt;wt&lt;/sup&gt; can represent distinct subtypes of acute myeloid leukaemia disease, erasistrinid (IDH2 inhibitor) has been approved for use in relapsed or refractory IDH2-mutated acute myeloid leukaemia, and IDH1 inhibitors are in clinical development</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>5-15% (IDH1) and 10-20% (IDH2)</td>
<td>Conflicting reports on impact on survival</td>
<td>More common in NK acute myeloid leukaemia (&lt;30%) than in acute myeloid leukaemia with cytogenetic abnormalities, IDH1 and IDH2&lt;sup&gt;wt&lt;/sup&gt; are associated with concomitant NPM1 mutations, IDH1&lt;sup&gt;wt&lt;/sup&gt; can represent distinct subtypes of acute myeloid leukaemia disease, erasistrinid (IDH2 inhibitor) has been approved for use in relapsed or refractory IDH2-mutated acute myeloid leukaemia, and IDH1 inhibitors are in clinical development</td>
</tr>
<tr>
<td>NRAS</td>
<td>About 15%</td>
<td>Conflicting reports on impact on survival</td>
<td>Associated with NPM1 and biallelic CEBPA mutations, and with inv(16) or t(15;16) and t(3;3), superior outcomes with NRAS&lt;sup&gt;wt&lt;/sup&gt; mutation in presence of NPM1 and DNMT3A mutations, and RAS pathway inhibitors are in clinical development</td>
</tr>
<tr>
<td>TET2</td>
<td>5-20%</td>
<td>Conflicting reports on impact on survival</td>
<td>More common in NK acute myeloid leukaemia (&lt;25%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in older adults, CHIP mutation, mutually exclusive with IDH1 and IDH2 mutations</td>
</tr>
<tr>
<td>ASXL1</td>
<td>5-15%</td>
<td>Inferior survival</td>
<td>Increased incidence in older adults, CHIP mutation, associated with secondary acute myeloid leukaemia that has progressed from antecedent haematologic malignancy</td>
</tr>
<tr>
<td>RUNX1</td>
<td>5-20%</td>
<td>Inferior survival</td>
<td>Increased incidence in older adults, associated with secondary acute myeloid leukaemia that has progressed from antecedent haematologic malignancy, and germline mutations with familial predisposition to acute myeloid leukaemia have been described</td>
</tr>
<tr>
<td>TP53</td>
<td>5-20%</td>
<td>Inferior survival</td>
<td>Increased incidence in older adults, and associated with complex karyotype, monosomy karyotype, and secondary acute myeloid leukaemia (from antecedent haematological malignancy or therapy related)</td>
</tr>
</tbody>
</table>

ITD=internal tandem duplication. TKD=tyrosine kinase domain. NK=normal karyotype. CBF=core-binding factor. CHIP=clonal haemopoiesis of indeterminate potential.
Beat AML

- Functional Genomic Landscape of AML
  - [http://www.vizome.org/aml/](http://www.vizome.org/aml/)

Tyner et al, Nature 562: 526, 2018; Benard et al, Leukemia 33:826, 2019
Algorithms for AML

• Easiest algorithm is to just refer patients to a teaching hospital with expertise

• 6 physicians
• 5 APPs
• 2 pharmacists
• 22 bed floor
• 6 OPD nurses
• Social workers
• 160-180 pts/year