New and Emerging Treatments in Acute Myeloid Leukemia

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Disclosures

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I will designate FDA-approved drugs for disease conditions and drugs that are under clinical investigation
Objectives

• Provide a general overview of acute myeloid leukemia (AML)

• Review current diagnostic workup and treatment approaches in AML

• Discuss new management strategies that are being investigated in AML
Acute Myeloid Leukemia (AML)

- Most common form of acute leukemia in adults
- ~20,000 new diagnoses and ~10,000 deaths on a yearly basis
- Median age of diagnosis: 65 years old
AML Diagnosis and Characterization

- Demonstration of 20% or more myeloid blasts on peripheral blood smear OR bone marrow biopsy
  - Common additional testing includes cytogenetics (analysis of chromosomes), mutational testing, and consideration for testing of hereditary cancer syndromes

- **De novo AML**: AML diagnosed without a previous diagnosis of hematologic disorder or prior exposure to cytotoxic drugs and/or radiation therapy

- **Secondary AML (sAML)**: AML diagnosed in a patient with a pre-existing hematologic disorder such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN)

- **Therapy-related AML (t-AML)**: AML diagnosed in a patient previously treated with cytotoxic therapy or radiation therapy

WHO 2016 Criteria; Soulier, Blood 2020
Standard Treatment Options pre-2017

- Intensive Induction Chemotherapy
  - Examples: Cytarabine + anthracycline (“7+3”), FLAG + Idarubicin

- Non-intensive treatment approaches
  - Examples: Azacitidine, Decitabine, Low-dose cytarabine

- Supportive care
FDA-approved Treatment Options in the Current Era

Combined with induction therapy

Midostaurin
FLT3 inhibitor
28-April-2017

Typically combined with induction therapy

Daunorubicin - Cytarabine
Liposomal Chemotherapy
03-August-2017

Approved for secondary AML

Gemutuzumab Ozogamicin
Anti-CD3 antibody/drug conjugate
01-September-2017

Utilized in non-intensive approaches

Venetoclax
BCL-2 Inhibitor
21-November-2018

Ivosidenib
IDH-1 Inhibitor
02-May-2019

Oral
Azacitidine
Nucleoside analogue
01-September-2020

Glasdegib
Hedgehog Inhibitor
21-November-2018

Maintenance after consolidation

Enasidenib
IDH-2 Inhibitor
01-August-2017

Ivosidenib
IDH-1 Inhibitor
20-July-2018

Gilteitinib
FLT3 inhibitor
28-November-2018

Newly diagnosed

Relapsed / Refractory
What Factors Determine Initial AML Treatment?

- Cytogenetic and Molecular Characteristics of disease
- Other medical conditions a patient may have
- Patient input/preferences!
Treatment Approach in Newly-Diagnosed AML
disease and patient characteristics
consideration for clinical trials

Appropriate for intensive chemotherapy
- t-AML or AML with myelodysplasia-related changes
  - CPX-351
  - 7+3+ gemtuzumab ozogamicin
  - 7+3+midostaurin
- core-binding factor AML
- FLT3 mutation
  - 7+3
- other AML
  - CPX-351
  - 7+3+midostaurin
  - 7+3
  - ivosidenib or hypomethylating agent + venetoclax
  - hypomethylating agent + venetoclax
  - low-dose cytarabine + venetoclax

Appropriate for non-intensive treatment approaches
- IDH1 mutation
- other AML
- IDH1 mutation
- other AML

Cahill et al, Advances in Oncology 2021
Treatment Approaches in Complete Remission

- **CR after intensive induction**
  - Consolidation therapy
  - Considerations for transplant if intermediate/high-risk disease
  - Consideration for CC-486 (oral azacitidine) after consolidation if intermediate/high-risk disease but not proceeding with transplant

- **CR after non-intensive approach**
  - Continue cycles of therapy indefinitely, dose adjustments may be considered
Emerging Treatment Strategies

- Intensive induction combination therapies
  - Venetoclax
  - Ivosidenib
  - Enasidenib
  - Gilteritinib

- Non-intensive combination therapies
  - HMA + Ven + FLT3 inhibitors
  - HMA + Ven + IDH Inhibitors

- Oral regimens in AML

- Therapies in TP53-mutated AML

*under clinical investigation but not yet FDA-approved!
## FLAG-Ida + Venetoclax in New AML and R/R AML

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (N = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, No. (% [CI])</td>
<td>56 (82 [71 to 91])</td>
</tr>
<tr>
<td>CRc (CR + CRi + CRh), No. (% [95% CI])</td>
<td>52 (76 [65 to 86])</td>
</tr>
<tr>
<td>CR, No. (%)</td>
<td>37 (53)</td>
</tr>
<tr>
<td>CRh, No. (%)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>CRi, No. (%)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>MRD⁻ CR (flow cytometry), No. (% [95% CI])</td>
<td>43 (83 [70 to 92])</td>
</tr>
<tr>
<td>MLFS</td>
<td>4</td>
</tr>
<tr>
<td>No response</td>
<td>12</td>
</tr>
<tr>
<td>DOR (median, months)</td>
<td>NR</td>
</tr>
<tr>
<td>EFS</td>
<td>18 (10.1 to NE)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>18 (10.1 to NE)</td>
</tr>
<tr>
<td>6-month, % (95% CI)</td>
<td>70 (59 to 81)</td>
</tr>
<tr>
<td>12-month, % (95% CI)</td>
<td>56 (44 to 71)</td>
</tr>
<tr>
<td>OS</td>
<td>NR</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>NR</td>
</tr>
<tr>
<td>6-month, % (95% CI)</td>
<td>81 (71 to 91)</td>
</tr>
<tr>
<td>12-month, % (95% CI)</td>
<td>70 (58 to 83)</td>
</tr>
</tbody>
</table>
IDH Inhibition + Intensive Induction Chemotherapy in Newly-Diagnosed *IDH*-mutated AML

Ivosidenib or Enasidenib Combined with Intensive Chemotherapy in Newly Diagnosed AML

Induction (1-2 cycles)
- Continuous IVO 500 mg QD
- Continuous ENA 100 mg QD

Consolidation (≤ 4 cycles)
- Continuous IVO 500 mg QD
- Continuous ENA 100 mg QD

Maintenance*
- Continuous IVO 500 mg QD
- Continuous ENA 100 mg QD

*Until relapse, development of unacceptable toxicity, or allogeneic HSCT

Best Response at Any Time

Stein et al, Blood 2021
Gilteritinib + Intensive Induction Chemotherapy in Newly-diagnosed *FLT3*-mutated AML

Table 2. Clinical Response to Gilteritinib in Combination with 7+3 Induction and Consolidation Chemotherapy at the End-of-Induction Time Point in *FLT3*mut⁺ Patients with Newly Diagnosed AML Who Received Gilteritinib 120 mg/d

<table>
<thead>
<tr>
<th>Response Parameter, a n (%)</th>
<th><em>FLT3</em>mut⁺ Patients who Received 120 mg/d (N=38)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>15 (39.5)</td>
</tr>
<tr>
<td>CRp</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>CRi</td>
<td>15 (39.5)</td>
</tr>
<tr>
<td>CRc</td>
<td>31 (81.6)</td>
</tr>
</tbody>
</table>
Select HMA+ Venetoclax Triplet Therapies in Trials

<table>
<thead>
<tr>
<th>Drug Added</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilteritinib</td>
<td>FLT3</td>
</tr>
<tr>
<td>Quizartinib</td>
<td>FLT3</td>
</tr>
<tr>
<td>Ivosidenib</td>
<td>IDH1</td>
</tr>
<tr>
<td>Enasidenib</td>
<td>IDH2</td>
</tr>
</tbody>
</table>
Decitabine-Cedazuridine and Oral Combinations

**Investigational agent(s)** | **Patient population** | **Trial number**
--- | --- | ---
ASTX030 | MDS, CMML, AML | NCT04256317
ASTX030 | MDS | NCT04608110
ASTX727 | Lower-risk MDS | NCT03502668, NCT03906695
ASTX727 | MDS with detectable MRD after allo-HCT | NCT04742634
ASTX727 + itacitinib, INCB053914, or INCB059872 | MDS/MPN overlap syndromes | NCT04061421
ASTX727 + venetoclax | MDS, CMML | NCT04655755
ASTX727 + venetoclax | AML | NCT04657081, NCT04746235
ASTX727 + venetoclax + ivosidenib orenasidenib | IDH1 or IDH2-mutated AML | NCT04774393
ASTX727 + ASTX660 | AML | NCT04155580
Immunotherapy in AML
Pembrolizumab in R/R AML

38% CR Rate
Novel Therapies in *TP53*-mutated AML

Table 1. Clinical trials in *TP53* myeloid malignancies.

<table>
<thead>
<tr>
<th>Treatments (NCI Number)</th>
<th>Phase</th>
<th>Number of Patients</th>
<th>Overall Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + VEN NCT04401748</td>
<td>3</td>
<td>431 AML patients total</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>286 (AZA + VEN) (23% <em>TP53</em> mutated)</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>145 (AZA + Placebo) (16% <em>TP53</em> mutated)</td>
<td>0%</td>
</tr>
<tr>
<td>AZA + Eprenetapopt NCT03072040</td>
<td>1b/2</td>
<td>55 <em>TP53</em> mutated MDS/AML patients</td>
<td>71%</td>
</tr>
<tr>
<td>AZA + Eprenetapopt NCT03588078</td>
<td>2</td>
<td>52 <em>TP53</em> mutated MDS/AML patients</td>
<td>62%</td>
</tr>
<tr>
<td>AZA + MAGRO NCT03248479</td>
<td>1b</td>
<td>29 <em>TP53</em> mutated AML patients</td>
<td>59%</td>
</tr>
</tbody>
</table>

Table 2. Clinical trials ongoing in *TP53* myeloid malignancies.

<table>
<thead>
<tr>
<th>Treatments (NCI Number)</th>
<th>Phase</th>
<th>Number of Patients</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENHANCE-2</td>
<td>3</td>
<td>346 <em>TP53</em> mutated AML patients to be randomized</td>
<td>OS</td>
</tr>
<tr>
<td>AZA + MAGRO vs. AZA + VEN NCT04778397</td>
<td>3</td>
<td>154 <em>TP53</em> mutated MDS patients included</td>
<td>CR</td>
</tr>
<tr>
<td>AZA + Placebo vs. AZA + Eprenetapopt NCT03745716</td>
<td>3</td>
<td>51 <em>TP53</em> mutated AML patients</td>
<td>Safety</td>
</tr>
<tr>
<td>AZA + VEN + Eprenetapopt NCT04214860</td>
<td>1</td>
<td>100 <em>TP53</em> mutated AML patients</td>
<td>RFS</td>
</tr>
<tr>
<td>DAC + Cytarabine + ATO NCT03381781</td>
<td>2</td>
<td>33 <em>TP53</em> MDS/MAL patients included</td>
<td>RFS</td>
</tr>
</tbody>
</table>
Summary

• Since 2017 there have been a number of newly-approved therapies for AML

• Current treatment considerations should factor in disease characteristics and patient characteristics

• Novel treatment strategies include:
  • Combination approaches of FDA-approved drugs
  • All oral regimens
  • Immunotherapy
  • Approaches specific to TP53-mutated AML
Thank you!