High Risk MDS to AML

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AAMDS 2020 Virtual Spring Conference
April 25, 2020
Agenda

• What is the difference between AML and MDS?

• How does MDS evolve to AML and can this be prevented?

• How does one know when MDS progresses to AML?

• Prognosis

• Treatment
Possible Outcomes for MDS Patients

MDS

- Behaves Itself
  - Requires Treatment
    - Patient Dies of non-MDS Cause
  - Does Not Require Treatment
- Does Not Behave Itself
  - Dies from MDS Complication
  - Evolves to Acute Myeloid Leukemia
How to Distinguish AML from MDS

**MDS**
- Myeloid cancer
- Affects the bone marrow
- Causes abnormal blood counts
- Less than 20% of the bone marrow (or peripheral blood) are **blasts**

**AML**
- Myeloid cancer
- Affects the bone marrow
- Causes abnormal blood counts
- Greater than 20% of the bone marrow (or peripheral blood) are **blasts**
What are Blasts?
Can Progression of MDS to AML be Prevented?

- For patients who require treatment for MDS, thin evidence to support the use of a hypomethylating agent (azacitidine or decitabine) can prevent progression.

- For patients who do not require treatment for MDS, no evidence that treating them can prevent progression.

- No lifestyle or environmental factors implicated in the progression of MDS to AML.

Silverman et al, Cancer 2011
How Can You Know When MDS Progresses?

• Bone marrow biopsy is the gold standard
  • Occasionally will see >20% blasts in the peripheral blood, or an increase in peripheral blood blasts or the appearance of peripheral blood blasts

• Changing blood counts
  • Worsened anemia, decreased platelets and/or white blood cells
  • Increasing white blood cell count

• Symptoms
  • Worsened fatigue, bruising, bleeding or infections
  • None
How Likely is MDS to Progress to AML? IPSS-R

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categories and Associated Scores</th>
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<tbody>
<tr>
<td>Cytogenetic risk</td>
<td>Very good</td>
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<tr>
<td>IPSS-R: Prognostic Risk Category Clinical Outcomes*</td>
<td></td>
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<tr>
<td>Patients (%)</td>
<td>No. pts</td>
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<tr>
<td></td>
<td>7012</td>
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<td>Survival***</td>
<td>8.8</td>
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<tr>
<td>AML/25%***,^</td>
<td>NR</td>
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<tr>
<td>Abs. neutrophil count (x 10^9/L)</td>
<td>≥0.8</td>
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https://www.mds-foundation.org/ipss-r-calculator/
“Secondary AML” is AML from MDS

• ~25-30% of all AML patients

• More likely to be older

• More likely to resist treatment or relapse after a response

• Historically, prognosis has been poor

• Worse outcomes compared to “de novo” AML

Oliai et al, BJH 2020
Treatment Options

• Intensive approaches
  • Induction chemotherapy
  • CPX-351

• Less-intensive approaches
  • Hypomethylating agents
  • Genomically-targeted therapies
  • Non-genomically targeted therapies

• Allogeneic stem cell transplantation
Intensive Chemotherapy

• “7+3” and similar regimens
  • Only for candidates likely to tolerate this therapy
  • More likely to be refractory or to relapse after treatment

• Liposomal daunorubicin-cytarabine (CPX-351)
  • Better outcomes than 7+3
  • Survival ~9 months

Lancet et al, JCO 2018
Hypomethylating Agents

- Azacitidine or decitabine*
  - Remission rate 18-28%
  - Remission duration ~10 months
  - Takes 4-6 months to know if effective
  - Well tolerated
  - Overall survival 8-10 months

*For all AML, not just secondary, so assume outcomes for secondary AML are worse than shown here
Genomically-Targeted Therapies

**FLT3**
- No approved FLT3 inhibitors for newly diagnosed AML patients who are not getting intensive induction chemotherapy
- Use midostaurin with induction chemotherapy if FLT3+ and suitable for induction
- FLT3 incidence is low in secondary AML

**IDH**
- IDH1 inhibitor ivosidenib approved as a single agent for IDH1+ newly diagnosed AML patients
- IDH2 inhibitor enasidenib not approved but has equivalent efficacy
- 20% incidence in AML in general; much lower in secondary AML

Stone et al, NEJM 2017
Roboz et al, Blood 2020
Pollyea et al, Leukemia 2019
Non-Genomically Targeted Therapy #1: Glasdegib

• Inhibitor of the Hedgehog signaling pathway
• Oral, combine with low-dose cytarabine
• In newly diagnosed AML patients deemed poor candidates for intensive induction chemotherapy, overall survival was about 8 months
• Responses not broken down according to secondary vs de novo AML

Cortes et al, Leukemia 2018
Non-Genomically Targeted Therapy #2: Venetoclax

- Inhibitor of the protein BCL-2
- High response rates (~70%) when combined with azactidine/decitabine in newly diagnosed AML
- Overall survival ~16 months

DiNardo et al, Blood 2019
Pollyea et al, ASH 2018
Accounting for the Impact of a Prior Therapy for MDS on Venetoclax Response

Prior hypomethylating agent associated with worse response rates

Winters et al, Blood Advances, 2019

Wei et al, JCO 2019
Allogeneic Stem Cell Transplantation

• The only potentially curative option

• Improves outcomes compared to those who do not get a transplant (but complicated by bias)

• However, ~30% likely die from a transplant related complication

Oliai et al, BJH 2020
Conclusions

• MDS can evolve to AML
  • This outcome is not within the control of any individual
  • Requires a bone marrow biopsy to confirm

• Predictive scores can help assess risk of this occurring

• Historical outcomes have been poor
  • Now more therapeutic options
  • Lots of optimism for improvement
Thank You!