Acute myeloid leukemia and related myeloid neoplasms: WHO 2008 brings us closer to understanding clinical behavior

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Steven Devine, MD
The Ohio State University

Common Presentations of AML
• vague history of chronic progressive lethargy
• 1/3 of patients with acute leukemia will be acutely ill with significant skin, soft tissue, or respiratory infection.
• Petechiae with or without bleeding may be present
• Leukemias with a monocytic component may have gingival hypertrophy from leukemia infiltration/extramedullary involvement (of CNS, gums, skin, other)

But usually we don’t know why…
• An increased incidence of AML is associated with certain congenital conditions like Down syndrome, Bloom’s syndrome, Fanconi’s anemia
• Patients with acquired diseases such as myelodysplastic syndromes, myeloproliferative disorders, and other pre-leukemic states may progress to AML
• A variety of environmental factors, both work/treatment-related may cause the disease
  • exposure to ionizing radiation
  • chemical exposure to benzene, and possibly hydrocarbons
  • treatment with alkylating agents, topoisomerase inhibitors

Lab Findings in AML
• The hematocrit is generally low but severe anemia is uncommon
• The peripheral white blood cell count may be increased, decreased, or normal.
  – Approximately 35% of all AML patients will have ANC < 1,000/uL; circulating blast cells may be absent 15% of the time
• Disseminated intravascular coagulation (DIC) is common, it is nearly universal in acute promyelocytic leukemia
• Thrombocytopenia is frequently observed– platelet counts <20,000/uL are common, often leads to bruising or bleeding (gums, petechiae)

Basics of AML
• Approximately 9,000 new cases yr in US
• Incidence of AML rises with advancing age
• The median age is 65
  – Most children with leukemia have ALL (not AML)
• AML is about 80% of adult acute leukemias

Outcomes for AML patients are poor, few older patients (those age>60) survive 5 years

Outcomes for younger AML patients

For older patients (>60 years)

Byrd, et al, Blood 2002 (CALGB)

Farag, et al, Blood 2006 (CALGB)
Outcomes worse if:

- Older age (>60)
- High WBC (over 20,000/uL)
- Prior hematologic disorder like myelodysplastic syndrome
- Leukemia caused by prior chemotherapy
- Poor initial response to chemotherapy
- Poor performance status
- ADVERSE RISK CYTOGENETICS

How can we improve outcomes for AML patients?

Clinical understanding of disease goes only so far

How can we begin to tell that one AML is different from another (in terms of likelihood that our treatment will work)?

French-American British (FAB) Classification for AML

<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>Name</th>
<th>% of adult AML patients</th>
<th>Prognosis compared to average for AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Undifferentiated acute myeloblastic leukemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
<tr>
<td>M1</td>
<td>Acute myeloblastic leukemia with minimal maturation</td>
<td>15%</td>
<td>Average</td>
</tr>
<tr>
<td>M2</td>
<td>Acute myeloblastic leukemia with maturation</td>
<td>25%</td>
<td>Better</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia</td>
<td>10%</td>
<td>Best</td>
</tr>
<tr>
<td>M4</td>
<td>Acute monoblastic leukemia with eosinophilia</td>
<td>5%</td>
<td>Better</td>
</tr>
<tr>
<td>M4-eos</td>
<td>Acute monoblastic leukemia</td>
<td>10%</td>
<td>Average</td>
</tr>
<tr>
<td>M5</td>
<td>Acute monocytic leukemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroid leukemia</td>
<td>5%</td>
<td>Worst</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryoblastic leukemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
</tbody>
</table>

The only way to make a leap forward in improving outcomes in AML...

...understand the molecular biology of the disease(s).

...understand the reality that each AML case is unique. Treating all cases the same is doomed to fail.
Prognostic value of single gene mutations for subsets of AML (partial list)

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>Prognostic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1</td>
<td>Favorable in absence of FLT3 ITD</td>
</tr>
<tr>
<td>FLT3 ITD</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>FLT3 TKD</td>
<td>Controversial</td>
</tr>
<tr>
<td>CEBPA</td>
<td>Favorable</td>
</tr>
<tr>
<td>MLL PTD</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Ras</td>
<td>Neutral</td>
</tr>
<tr>
<td>WT-1</td>
<td>Controversial</td>
</tr>
<tr>
<td>RUNx1</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>

Cytogenetic/Molecular Risk Stratification for 2010

- **Favorable**
  - t(8;21)(q22;q22); RUNX1–RUNX1T1
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB–MYH11
  - Mutated NPM1 without FLT3–ITD (normal karyotype)
  - Mutated CEBPA (normal karyotype)
- **Intermediate-I**
  - All other combinations of FLT3 and NPM1
- **Intermediate-II**
  - t(1;11)(p22;q23); MLLT3-MLL
  - Cytogenetic abnormalities not classified as favorable or adverse
- **Adverse**
  - inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1–EVI1
  - t(6;9)(p23;q34); DEK–NUP214
  - t(v;11)(v;q23); MLL rearranged
  - -5 or del(5q); -7, del(7q);
  - complex karyotype; monosomal karyotype

Adapted from Dohner et al, Blood 2010

Major cytogenetic subgroups of AML and associated gene mutations

If you were the patient, what would sound better?

“History tells us that you are likely to do poorly with conventional treatment, but its all we have so let’s give it a try anyway.”

“History tells us that you are likely to do poorly with conventional treatment, so we have altered your treatment plan to mitigate this risk and improve your chances.”

Quick terminology for AML

- **Induction chemotherapy**
  - patient with leukemia about to be treated
- **Consolidation chemotherapy**
  - pt in complete remission at last testing, no evidence of disease (patient has already gone home, and this is planned at the follow up visit)

Treatment/Induction

- **Supportive care as discussed**
- **7+3**
  - 7 days of Ara-c by continuous infusion
  - 3 days of an anthracycline (pending eval of EF)
  - A third drug, etoposide, may be added too
- **Inpatient care for induction usually required**
- **Remission occurs in 60-80% of patients**
More terminology
- **Complete response (CR)**:
  - ANC >1000, Pt>100, RBC independence
  - maturation of all hematopoietic cell lines
  - less than 5% blasts
  - No other signs or symptoms of disease
- Leukemic burden $10^{12}$ reduced to $10^9$, additional (consolidation) therapy is required or patients will universally relapse

Typical course of AML induction
- In house about a month
- Older patients fare far worse in terms of response as well as treatment-related morbidity/mortality
- Most patients develop febrile neutropenia and have transfusion dependence
- Repeat Bone Marrow at count recovery

Consolidation
- Varying opinions in required number of consolidations or "cycles" needed, but we do know it is required as without it nearly all patients relapse
- Typically first consolidation occurs 2-3 weeks after count recovery from induction
- Subsets of patient do far better
  - when **High Dose Ara-c (HiDAC)** is given
- Allogeneic transplantation may be employed for those with the high risk of relapse, even in first remission; and after relapse

5 years without relapse after high dose Ara-C

- Inv 16
- t(8,21)
- Normal Cytog
- Adverse Cytog

Bloomfield, et al. 1998

What should we do with high risk AML patients?

How do we integrate the prognostic/predictive information in AML?

- Individualized Treatment
- Gene profiles
- miRNA profiles
- Single-gene marker
- Cytogenetics
- Age, clinical factors
- Genome sequencing?
How can we use prognostic information more effectively in 2010?

Use cytogenetics and molecular risk to guide choices for therapy

- Chemotherapy
- Role of allogeneic stem cell transplantation for patients in first complete remission (CR1)
- We need better therapies targeting unique molecular aberrations for each patient!

Use of cytogenetics to select therapy

Patients with "core-binding factor" (CBF) fusion genes have better survival when they receive repeated cycles of high dose cytosine arabinoside (ara-c) after they achieve remission. This is called consolidation therapy.

Bloomfield, et al. 1998, depicted are all patients, but benefit to higher dose was due to CBF patients

That’s why they are in the "favorable" risk group

Role of transplantation

- Allogeneic hematopoietic cell transplant (AlloHSCT) is the single most effective therapy currently available for the prevention of relapse

- But, AlloHCT is still risky and many treating physicians remain reluctant to recommend in CR1 until mortality rates can be substantially lowered

AlloHCT for AML Patients <60 years in CR1

- Adverse risk cytogenetics
  - Most agree allograft appropriate consolidation at least up to 55-60 years of age (Those >60 years require novel transplantation techniques in order to survive the process)
  - No role for transplant

- Intermediate risk cytogenetics
  - This is where it gets complicated
  - Recent meta-analyses suggest benefit for transplant, but debate rages...
    - Cornellison et al, Blood, 2007
    - Koreth et al, JAMA, 2009

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Outcomes in AML patients over 60 years of age based on karyotype at diagnosis...POOR

In treating older AML patients with standard therapy, the combination of low efficacy and high toxicity is not terribly appealing...

Can subsets be identified that will do better than others with intensive therapy?

Treating the “older” AML patient

- Who should be treated “intensively”? Subsets who are likely to do better than most...
  - Core binding factor (CBF) AML
  - Those with NPM1 gene mutations

- Consider alternative (experimental) therapy if:
  - Comorbid disease
  - Age >70
  - Borderline functional status
  - Cytogenetic adverse risk

Myelodysplastic syndromes (MDS)

MDS: Characteristics

- Clonal bone marrow disorders usually with hypercellular marrow, low counts, and cell function abnormalities
  - “Ineffective erythropoiesis”, resources being used but the final product is essentially non-functional

- Natural history is highly variable
  - Typical presentation is older patient with fatigue and anemia, often patients are treated inappropriately for iron deficiency initially
  - Can progress to AML, often fatal even if it does not due to high risk of infection over time

- No cure except for allogeneic transplantation, but most patients are elderly and not candidates

MDS: Clinical Overlap/Associations

PNH
MDS
AA
MDS
LGL
MDS
AML
PRCA
MPD
Myelodysplastic Syndromes

- Refractory cytopenia with unilineage dysplasia (RCUD)
  - Refractory anemia (RA)
  - Refractory neutropenia (RN)
  - Refractory thrombocytopenia (RT)
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with excess blasts (RAEB)
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable (MDS,U)
- Childhood myelodysplastic syndrome
  - Provisional entity: Refractory cytopenia of childhood (RCC)

Significant changes in the diagnosis and classification of MDS

- Patients with refractory cytopenia(s) suspected to have MDS, but who lack diagnostic morphologic features may be considered to have presumptive evidence of MDS if they have specific MDS-related cytogenetic abnormalities.
- An over-arching category of MDS, refractory cytopenia with unilineage dysplasia, has been added to incorporate patients who exhibit unilineage dysplasia associated with refractory anemia (unilineage erythroid dysplasia), refractory neutropenia (unilineage dysgranulopoiesis), or refractory thrombocytopenia (unilineage dysmegakaryopoiesis), and who have fewer than 1% blasts in the blood and fewer than 5% in the bone marrow.
**Significant changes in the diagnosis and classification of MDS**

- The category of refractory cytopenia with multilineage dysplasia is no longer subdivided according to whether 15% or more of the erythroid precursors are ring sideroblasts (RS), that is, the former category of RCMRD-RS is now incorporated in RCMRD.

- Patients with 2% to 4% blasts in the blood and less than 5% blasts in the bone marrow should be diagnosed as having RAEB-1 if other clinical and laboratory findings of MDS are present.

- A provisional entity, refractory cytopenia of childhood (RCC), has been added to include children with cytopenia(s) with less than 2% blasts in the peripheral blood and less than 5% in the bone marrow and evidence of dysplasia in 2 or more lineages. For children with 2% to 19% blasts in the blood and/or 5% to 19% in the bone marrow, the MDS subclassification should be made using the same criteria used for adults.

**Acute Myeloid Leukaemia Related Myeloid Neoplasms**

- Acute myeloid leukaemia with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22), RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
  - AML with t(15;17)(q22;q12); PML-RARA
  - AML with t(9;11)(p22;q23); MLT3-MLL
  - AML with t(6;9)(p23;q34); DEK-NUP214
  - AML with inv(3)(q21q26.2) or t(3;3)(q26.2); RPN1-EVI1
  - AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
  - Provisional entity: AML with mutated NPM1
  - Provisional entity: AML with mutated CEBPA

**Major Changes in AML category**

- As in the previous edition, AML with t(8;21)(q22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), and APL with t(15;17)(q22;q12) are considered as acute leukemia regardless of blast count in the PB or BM, but in contrast to the previous edition, for AML with t(9;11)(p22;q23) or other 11q23 abnormalities, as well as for all other subgroups (except the rare instance of some cases of erythroleukemia) blasts of 20% or more of white blood cells in PB or of all nucleated BM cells is required for the diagnosis of AML.

- In APL with t(15;17)(q22;q12); PML-RARA, variant RARA translocations with other partner genes are recognized separately: not all have typical APL features and some have all-trans retinoic acid (ATRA) resistance.

**Acute myeloid leukaemia with myelodysplasia-related changes**

- Therapy-related myeloid neoplasms
AML with myelodysplasia-related changes

- The name was changed and expanded from "AML with multilineage dysplasia" to "AML with myelodysplasia-related changes."
- Cases of AML are assigned to this category if (1) they have a history of MDS or MDS/MPN and have evolved to AML, (2) they have a myelodysplasia-related cytogenetic abnormality, or (3) at least 50% of cells in 2 or more myeloid lineages are dysplastic.

Therapy-related myeloid neoplasms

- Cases are no longer subcategorized as "alkylating agent related" or "topoisomerase II-inhibitor related."

AML, Not Otherwise Specified

- Some cases previously assigned to the subcategory of AML, NOS as acute erythroid leukemia or acute megakaryoblastic leukemia may be reclassified as AML with myelodysplasia-related changes.
- Cases previously categorized as AML, NOS, acute megakaryoblastic leukemia should be placed in the appropriate genetic category if they are associated with inv(3)(q21q26.2) or t(3:3)(q21;q26.2); RPN1-EVI1, or AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1. Down syndrome–related cases are excluded from this category as well.

Myeloid proliferations related to Down syndrome

- This new category incorporates transient abnormal myelopoiesis as well as MDS and AML that is Down syndrome–related. MDS and AML related to Down syndrome are biologically identical and thus are considered together as "Myeloid leukemia associated with Down syndrome."

Blastic plasmacytic dendritic cell neoplasm

- This is a new category that includes most cases previously classified as blastic NK-cell lymphoma/leukemia or agranular CD4+ CD56+ hematodermic neoplasm; it is derived from a precursor of plasmacytoid dendritic cells.

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN)

- Chronic myelomonocytic leukaemia (CMML)
- Atypical chronic myeloid leukaemia, BCR-ABL 1 negative (aCML)
- Juvenile myelomonocytic leukaemia (JMML)
- Myelodysplastic/Myeloproliferative neoplasm, unclassifiable (MDS/MPN,U)
- Provisional entity: Refractory anaemia with ring sideroblasts and thrombocytosis (RARS-T)
Significant changes in the diagnosis and classification of MDS/MPN

- Some cases of CMML with eosinophilia are relocated to the category “Myeloid/lymphoid neoplasms with eosinophilia and PDGFRB rearrangement.”
- The category atypical CML has been renamed atypical CML, BCR-ABL1-negative to emphasize that it is not merely a variant of CML, BCR-ABL1-positive.
- RARS-T remains as a “provisional entity” classified as MDS/MPN, unclassifiable, RARS-T. The criteria have been modified to include refractory anemia, dyserythropoiesis in the bone marrow with ring sideroblasts accounting for 15% or more of erythroid precursors, and megakaryocytes with features resembling those in PMF or ET; the platelet threshold is lowered to 450 x 10^9/L.

Conclusions

- Never before have we had such powerful tools to deepen our understanding of AML and MDS
- No patient group has truly “favorable” risk with the possible exception of APL
- Heterogeneity of disease highlights the need to deepen our molecular understanding of pathogenesis to develop effective new treatments
  - And to find the patients who should OR should not receive a particular therapy
- One fits all is easier. But we’ve tried that for 30+ years--it’s just not very effective…the future is molecular biology