Proposed Changes to the WHO Classification of Acute Leukemias and Myeloid Disorders

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Revision of the 4\textsuperscript{th} edition

- Current “blue book” is part of the 4\textsuperscript{th} edition series, starting in 2008
- Needs updating, but WHO has not completed all 4\textsuperscript{th} edition books and will not allow 5\textsuperscript{th} edition to begin until entire 4\textsuperscript{th} edition series is complete
- Will allow an on-line and printed revision of the 4\textsuperscript{th} edition
Clinical Advisory Committee

• March 31 and April 1, 2014, Chicago, IL
  – Organized by Jim Vardiman and Michelle LeBeau
  – 50 invited participants (pathologists, cytogeneticists, hematologists) and for acute leukemia and myeloid neoplasms topics
  – 50 invited participants for lymphoid neoplasms

• Acute Leukemia and Myeloid Neoplasms CAC Co-Chairs Clara Bloomfield and Mario Cazzola

• A series of questions were proposed by the co-chairs and involved pathologists for discussion and vote by the CAC
Lymphoid CAC
Myeloid CAC
WHO Classification of Acute Leukemia and Myeloid Neoplasms (4th Edition; 2008)

- Myeloproliferative neoplasms
- Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1
- Myelodysplastic/myeloproliferative neoplasms
- Myelodysplastic syndromes
- Acute myeloid leukemia and related precursor neoplasms
- Acute leukemias of ambiguous lineage
- Precursor lymphoid neoplasms
WHO Classification of Acute Leukemia and Myeloid Neoplasms (4th Edition; 2008)

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Myeloproliferative Neoplasms

• Chronic myelogenous leukemia, $BCR-ABL1$ positive
• Chronic neutrophilic leukemia
• Polycythemia vera
• Primary myelofibrosis
• Essential thrombocythemia
• Chronic eosinophilic leukemia
• Mastocytosis
• Myeloproliferative neoplasm, unclassifiable
Chronic Myeloid Leukemia, *BCR-ABL1* positive

- Mostly unchanged
- **Definition of accelerated phase**
  - Will include development of TKI/therapy resistance
- **Definition of lymphoid blast crisis**
  - Any lymphoblast population in the blood should raise concern for blast crisis
  - >5% (aberrant) lymphoblasts in the marrow should be considered blast crisis
Chronic Neutrophilic Leukemia

- Rare disorder of sustained neutrophilia without reactive cause or evidence of other MPN
- Mutations
  - CSF3R T6181
    - Mutations disrupt the JAK-STAT pathway and are considered disease defining for CNL
  - SETBP1, ASXL1
    - Frequent, but not disease specific

From Gotlib J. The Hematologist Sept 2013
Polycythemia Vera criteria (2008)

- Increased red cell production
  - Hemoglobin >18.5/16.5 g/dL in men/women
  - Hemoglobin >17/15 g/dL in men/women, with sustained increase of 2 g/dL over baseline
  - Increased red cell mass (>25% above normal)
  - Hemoglobin or hematocrit >99th percentile

- JAK2 mutation

  1. Bone marrow showing typical PV histology
  2. Decreased serum EPO levels
  3. Endogenous erythroid colony formation

Minor
Proposed revision to PV criteria

• Increased red cell production
  – Hemoglobin >16.5/16.0 g/dL in men/women or hematocrit >49/48% in men/women
  – Hemoglobin >17/15 g/dL in men/women, with sustained increase of 2 g/dL over baseline
  – Increased red cell mass (>25% above normal)
  – Hemoglobin or hematocrit >99%le

• Bone marrow showing typical PV histology

• JAK2 mutation

  1. Decreased serum EPO levels
  2. Endogenous erythroid colony formation
Primary Myelofibrosis and Essential Thrombocythemia

- Addition of CALR mutations to diagnostic criteria for both and MPL for ET
- Lower fibrosis requirement for prefibrotic/early PMF
  - Provide more information on the ddx of prePMF vs ET
Myeloproliferative Neoplasms

- Chronic myeloid leukemia, *BCR-ABL1* positive
- Chronic neutrophilic leukemia
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- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia
- Mastocytosis
- Myeloproliferative neoplasm, unclassifiable
Myelodysplastic Syndromes (2008)

- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
  - RAEB-1
  - RAEB-2
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome
  - Refractory cytopenia of childhood
Myelodysplastic Syndromes – Revised Terminology

- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
  - RAEB-1
  - RAEB-2
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome
  - Refractory cytopenia of childhood
- MDS with single lineage dysplasia
- MDS with ring sideroblasts with unilineage dysplasia
- MDS with ring sideroblasts with multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
  - With excess blasts-1
  - With excess blasts-2
- MDS with isolated del(5q)
- MDS, unclassifiable
- Childhood myelodysplastic syndrome
  - Refractory cytopenia of childhood
MDS with ring sideroblasts

- Frequent association with mutations of \textit{SF3B1} and a favorable prognosis with low risk of transformation to acute leukemia
- \(>15\%\) ring sideroblasts (among erythroid precursors), \textit{or}
- \(>5\%\) in the presence of an \textit{SF3B1} mutation
- Blast cell increases exclude this diagnosis
  - If multilineage dysplasia without a blast cell increase is present, case is classified as MDS with multilineage dysplasia with ring sideroblasts
Ring Sideroblasts and \textit{SF3B1} Mutations in MDS

Morphologic Review

- \textgreater{}5\% and \textless{}20\% Marrow Blasts
- \textless{}1\% Blood and \textless{}5\% Marrow Blasts

MDS with excess blasts
Ring Sideroblasts and SF3B1 Mutations in MDS

- **<1% Blood and <5% Marrow Blasts**
  - Iron Stain
  - **>15%**
  - **<15%**
    - **5-14%**
      - SF3B1
      - No
      - **<5%**
        - Single lineage
        - Dysplasia
        - Yes
        - Multilineage
          - Yes
          - MDS with ring sideroblasts (and unilineage dysplasia)
          - No
          - MDS with ring sideroblasts and multilineage dysplasia
          - MDS with single lineage dysplasia
          - MDS with multilineage dysplasia
MDS with Isolated del(5q)  
(5q-minus Syndrome)

• Currently restricted to del(5q) as the only abnormality  
• Will now allow a second (non-high risk; i.e. -7) cytogenetic abnormality  
• Cases with >2 abnormalities, multilineage dysplasia or increase blasts will not qualify for this category  
• Recommend TP53 mutation assessment or p53 staining

Germing Leukemia 26:1286, 2012; 
Erythroid/myeloid leukemia is now considered as MDS with excess blasts

• Prior definition of erythroleukemia (erythroid/myeloid type) in AML, NOS required ≥50% marrow erythroid precursors and ≥20% myeloblasts among non-erythroid cells
• These cases will now be classified as MDS based on the total blast cell count

Evaluation of Dysplastic Marrows with over 50% Erythroids

- >50% Marrow Erythroids
  - Determine Absolute Blast Cell Count
    - <5%
    - 5-19%
    - ≥20%
      - AML
      - MDS with excess blasts
      - Iron Stain Dysplasia
        - MDS with unilineage dysplasia (+/- ring sideroblasts)
        - MDS with multilineage dysplasia (+/- ring sideroblasts)
WHO Classification of Acute Leukemia and Myeloid Neoplasms (4th Edition; 2008)

- Myeloproliferative neoplasms
- Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1
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Familial Myeloid Neoplasms

- Familial MDS/AML is likely more prevalent than realized
- Familial MDS/AML associated with germline mutations
  - *CEBPA* (AML)
  - *SRP72* (AML)
  - *DDX41* (MDS/AML)
- Familial hematologic malignancies associated with platelet disorders and gene mutations
  - *RUNX1* (AML)
  - *ANKRD26* (AML)
  - *ETV6* (AL and solid tumors)
- Familial MDS/AML associated with other organ dysfunction
  - *GATA2* (MDS/AML)
  - *TERC/TERT*
  - DNA repair gene syndromes
  - Tumor suppressor gene syndromes

WHO Classification of Precursor Myeloid and Lymphoid Neoplasms (4th Edition)

**Acute myeloid leukemia (AML) and related precursor neoplasms**
- AML 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*)
  - Acute promyelocytic leukemia with t(15;17)(q24.1;q21.1) (*PML-RARA*)
  - AML with t(9;11)(p22;q23) (*MLLT3-MLL*)
  - AML with t(6;9)(p23;q34) (*DEK-NUP214*)
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;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*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML not otherwise specified
  - AML minimally differentiated
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic and monocytic leukemia
  - Acute erythroid leukemia
  - Acute megakaryocytic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
  - Myeloid sarcoma
  - Myeloid proliferations related to Down syndrome
  - Blastic plasmacytoid dendritic cell neoplasm

**Acute leukemias of ambiguous lineage**
- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*
- Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukemia, B/myeloid, NOS
- Mixed phenotype acute leukemia, T/myeloid, NOS
- Mixed phenotype acute leukemia, NOS, rare types
- Other ambiguous lineage leukemias

**Precursor lymphoid neoplasms**
- B-lymphoblastic leukemia/lymphoma, not otherwise specified
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B-lymphoblastic leukemia/lymphoma with t(v;11q23)(*MLL*)
  - B-lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) (*ETV6-RUNX1*)
  - B-lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) (*IL3-IGH*)
  - B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3) (*TCF3-PBX1*)
  - B-lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B-lymphoblastic leukemia/lymphoma with hypodiploidy
- T-lymphoblastic leukemia/lymphoma
2008 WHO Classification of AML

- AML 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)
  - Acute promyelocytic leukemia with t(15;17)(q24.1;q21.1) (PML-RARA)
  - AML with t(9;11)(p22;q23) (MLLT3-MLL)
  - AML with t(6;9)(p23;q34) (DEK-NUP214)
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;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

- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, not otherwise specified
  - AML minimally differentiated
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic and monocytic leukemia
  - Acute erythroid leukemia
  - Acute megakaryocytic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis

- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
Precursor Lymphoid Neoplasms (2008)

- B-lymphoblastic leukemia/lymphoma, not otherwise specified
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B-lymphoblastic leukemia/lymphoma with t(v;11q23)(MLL)
  - B-lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) (ETV6-RUNX1)
  - B-lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) (IL3-IGH@
  - B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3) (TCF3-PBX1)
- T-lymphoblastic leukemia/lymphoma
Since 2008

- Classification systems move slowly, but science does not
- Mutations
- Protein expression
- Methylation
Since 2008

• Classification systems move slowly, but science does not
• Next generation sequencing (NGS) has resulted in an explosion of new information
Advances in ALL

- **IKZF1** deletions
  - at 7p12 encodes the zinc finger transcription factor IKAROS
  - Associated with gene expression signature similar to Ph+ ALL
  - Very poor prognosis independent of age, WBC count and genetic subtype

- **JAK** mutations
- **CRLF2** translocations

Advances in ALL

- **IKZF1** deletions
- **JAK** mutations
  - **JAK1**, **JAK2** and **JAK3** mutations found in 10.7% of Ph-negative B-ALL (80% **JAK2**)
  - Mutations associated with deletion of **IKZF1** and **CDKN2A/B** and a Ph+ ALL gene expression profile
  - Very poor prognosis of **IKZF1** deleted/**JAK** mutated cases
- **CRLF2** translocations

Mullighan et al. PNAS 106;9414, 2009
Advances in ALL

- **IKZF1** deletions
- **JAK** mutations
- **CRLF2** translocations
  - Found in 7-14% of B-ALLs and in 53% of Down-syndrome associated ALL
  - Located at Xp22.3/Yp11.3
  - 62% are translocations with **IGH**
  - Associated with
    - **JAK1** and **JAK2** mutations
    - **IKZF1** deletions
    - Hispanic ethnicity
    - Very poor prognosis

Mullighan et al. Nat Genet 41:1243, 2009
Harvey et al. Blood 115:5312, 2010
**BCR-ABL1-like B-ALL**
(B-ALL with Translocations Involving Tyrosine Kinases or Cytokine Receptors)

- *BCR-ABL1*-like B-ALL is a high risk ALL with a gene expression profile similar to that of *BCR-ABL1*+ ALL
- Accounts for 10% of pediatric and 25% of adult ALL; poor clinical outcomes; may be amenable to targeted therapy
- Need to establish clear diagnostic criteria
  - *CRLF2* translocations
    - Usually show increased expression of CRLF2 by flow cytometry analysis
  - Some have activating mutations or rearrangements of genes, such as *ABL1, ABL2, JAK2, PDGFRB, NTRK3, TYK2, CSF1R*, and/or *EPOR*
    - Diagnostic significance of deletions/mutations of *IKZF1, CDKN2A/B, JAK1* less clear
  - The full spectrum of genetic changes is still being investigated

ALL with iAMP21

- Intrachromosomal amplification of chromosome 21 (iAMP21) accounts for about 2% of B-ALL
- Generally in older children (median age 9 years) with lower WBC count
- Adverse outcomes when treated with standard risk therapy; but improved when treated as high risk ALL
- Presence of 5 or more copies of RUNX1 on a single cell or 3 or more extra copies on a single abnormal chromosome 21
- Reliably detected by FISH for RUNX1 and confirmed by cytogenetics

Harrison et al. Leukemia 28:1015, 2014
B-lymphoblastic leukemia/lymphoma with hypodiploidy

- Low hypodiploid (32-39 chromosomes) and near haploid (24-31 chromosomes) B-ALL have a worse prognosis than near diploid cases and are likely distinct entities.
- Near haploid ALL is often associated with RAS and receptor TK signaling mutations.
- >90% of low hypodiploid cases have TP53 mutations and often have alterations of IKZF2 and RB1.
- 43% of low hypodiploid ALL have germline TP53 mutations.

Early T-Precursor Acute Lymphoblastic Leukemia (ETP-ALL)

- Early T-Precursor (ETP) ALL comprises 10-15% of T-ALL
- Defined immunophenotypically by expression of cCD3, CD7, low CD5, but no CD1a, CD4 or CD8
  - Expresses CD34 and myeloid-related antigens (CD117, CD33, or CD13) but not MPO
- Thought to arise from an early progenitor cell with lineage plasticity that may be more closely related to human stem cells than to early T-cell precursors
- Molecular genetics
  - Increase in AML-associated mutations
  - Rare NOTCH pathway (T-ALL-associated) mutations
- Initially considered high risk due to higher rate of induction failure
- Recent COG study showed no outcome difference with current T-ALL therapy

- Wood B, et al. ASH Abstract #1, 2014
Proposed WHO Revisions for ALL

- **B-ALL**
  - *BCR-ABL1*-like B-ALL
  - B-ALL with iAMP21
  - Hypodiploid ALL will be subdivided
    - Near haploid
    - Low hypodiploid
    - Near diploid

- **T-ALL**
  - Early T-Precursor ALL
AML with Multilineage Dysplasia

AML with inv(3) or t(3;3)

AML with t(6;9)

AML with Myelodysplasia-Related Changes

AML, Not Otherwise Categorized

History and/or cytogenetics

NPM1 and CEBPA

AML with mutated NPM1
AML with mutated CEBPA

AML, Not Otherwise Specified
What about new translocations in AML?
AML with *BCR-ABL1*

- Difficult to distinguish from myeloid blast crisis of chronic myelogenous leukemia
  - Few basophils
  - Less splenomegaly
- Deletion of antigen receptors, particularly *IGH*, recently shown to be specific for de novo disease
  - Detection of t(9;22) in only blasts supports diagnosis
- Subset of cases have mutated *NPM1*
- Important to recognize due to presence of targeted (TKI) therapy

Mutations in AML

• Only four mentioned in 2008 WHO
  – Provisional entities
    • NPM1
    • CEPBA
  – Prognostic markers
    • FLT3
    • KIT
Cooperation between mutations in AML pathogenesis

Class I Translocations/Mutations
- FLT3-ITD
- FLT3-TKD
- KIT
- RAS
- PTPN11
- JAK2

Class II Translocations/Mutations
- PML-RARA
- RUNX1-RUNX1T1
- CBFB-MYH11
- MLL fusions
- CEBPA
- NPM1?

AML

proliferation and/or survival advantage; not affecting differentiation

impaired hematopoietic differentiation and subsequent apoptosis

Gilliland and Griffin, Blood 100:1532, 2002 (modified by H. Döhner)
AML with mutated CEBPA

- 7-20% of AMLs have mutations of CEBPA
  - More frequent with normal or intermediate karyotype
- 12.5-47% are single/monoallelic
- Double mutant/biallelic cases (CEBPA\textsuperscript{dm}) predict a favorable prognosis
  - Low frequency of other mutations or other cytogenetic abnormalities

**NPM1 and CEBPA Mutations in AML-MRC and Secondary AML**

- **Significance of multilineage dysplasia in the presence of NPM1 mutation, a normal karyotype and no history of MDS**
  - MLD found in 74/318 (23%) de novo NPM1 mutated AML
  - No prognostic significance for MLD (Falini et al. Blood 115:3776, 2010)

- **NPM1 mutations in secondary AML**
  - Approximately 16% of AMLs arising from MDS, post therapy or following an MPN or CMML have mutations
  - NPM1 mutation usually not present in original disease
  - Such cases lack the favorable prognosis of de novo AML with mutated NPM1

- **CEBPA mutations**
  - MLD found in 28/108 (25.9%) CEBPA mutated AML patients
  - No significant survival difference in MLD+ and MLD- groups

Döhner et al. Blood 106:3740, 2005
Schnittger et al Leukemia 25:615, 2011
Survival curves of patients up to 60 years with intermediate-risk cytogenetics AML depending on $NPM1$ status and presence of multilineage dysplastic features (MLD)


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AML with mutated \textit{NPM1} or \textit{CEPBA} and an abnormal karyotype

- Abnormal karyotype identified in 14.7\% of \textit{NPM1} and 26\% of \textit{CEBPA} mutated AML cases
- +8, +4, -Y, del(9q) and +21 most frequent with \textit{NPM1} mutation
- del(9q), del(11q), -Y, +10, +21 most frequent with biallelic \textit{CEBPA} mutation
- del(9q) is currently considered an MDS-related cytogenetic abnormality, but it appears to be unusually common in \textit{NPM1} and \textit{CEBPA} mutated cases
- In this setting, del(9q) does not appear to have prognostic significance

## Mutations in AML

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency in AML</th>
<th>Reported prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1</td>
<td>30-35%</td>
<td>Favorable</td>
</tr>
<tr>
<td>FLT3 ITD</td>
<td>25%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>15-25%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>NRAS/KRAS</td>
<td>15-20%</td>
<td>Neutral</td>
</tr>
<tr>
<td>WT1</td>
<td>10-15%</td>
<td>Neutral to unfavorable</td>
</tr>
<tr>
<td>RUNX1</td>
<td>10-15%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>IDH2 R132</td>
<td>7-16%</td>
<td>Variable</td>
</tr>
<tr>
<td>IDH2 R140 and R172</td>
<td>8-15%</td>
<td>Variable</td>
</tr>
<tr>
<td>TET2</td>
<td>8-12%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>MLL</td>
<td>5-10%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>ASXL1</td>
<td>3-19%</td>
<td>Unfavorable</td>
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<tr>
<td>FLT3 TKD</td>
<td>7%</td>
<td>Neutral</td>
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<tr>
<td>CEBPA</td>
<td>6%</td>
<td>Favorable</td>
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<tr>
<td>PTPN11</td>
<td>3%</td>
<td>Unknown</td>
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<td>PHF6</td>
<td>2-4%</td>
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</tr>
<tr>
<td>TP53</td>
<td>2-5%</td>
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</tr>
<tr>
<td>KIT</td>
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</tr>
<tr>
<td>CBL</td>
<td>1-3%</td>
<td>Unknown</td>
</tr>
<tr>
<td>EZH2</td>
<td>1-3%</td>
<td>Unknown</td>
</tr>
<tr>
<td>JAK2</td>
<td>1%</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>
AML with mutated RUNX1

- Gene located at 21q22
- Encodes the alpha subunit of the core binding factor
- Mutation in 4-16% of AML
- More frequent in older male patients
- Frequent prior history of MDS, or prior exposure to radiation
- Immature morphology and phenotype common
- Frequently associated ASXL1, KMT2A-PTD, (FLT3-ITD), IDH1\textsuperscript{R132}, and IDH2\textsuperscript{R140} and R172 mutations
- Rare CEBPA or NPM1 mutations
- Poor response to therapy with shortened survival

Proposed WHO Revisions for AML

- **AML, NOS**
  - Mostly unchanged
  - Move erythroid/myeloid type of acute erythroid leukemia to the MDS section

- **New cytogenetic subgroups**
  - Rare ones will be mentioned, but not added to the classification
  - AML with *BCR-ABL1*
    - Antigen receptor deletion
    - *BCR-ABL1* absent in background cells
  - Refine APL with *PML-RARA* fusion
Proposed WHO Revisions for AML

• New and revised mutation subgroups
  – AML with mutated RUNX1
    • Category will only include de novo cases
    • Cases arising from MDS will still be called AML-MRC
    • Cases with prior therapy will still be therapy-related AML
Proposed WHO Revisions for AML

- New and revised mutation subgroups
  - AML with \textit{RUNX1} mutation
  - AML with \textit{CEBPA} mutation will have to be heterozygous/double mutation
  - \textit{NPM1} and \textit{CEBPA}^{dm} mutations will trump multilineage dysplasia in de novo disease without MDS-related cytogenetic abnormalities other than del(9q)
Proposed WHO Revisions for AML

- Revise criteria for AML with myelodysplasia-related changes
  - Remove de novo cases with no MDS-related cytogenetic abnormalities if *NPM1* or \( \text{CEBPA}^{\text{dm}} \) mutated
  - Revise MDS-related cytogenetic abnormalities
    - Allow del(9q) only in the absence of *NPM1* and *CEBPA* mutation
MDS-related cytogenetic abnormalities

- **Complex karyotype***
- **Unbalanced abnormalities**
  - -7/del(7q)
  - -5/del(5q)/t(5q)
  - i(17q)/t(17p)
  - -13/del(13q)
  - del(11q)
  - del(12p)/t(12p)
  - del(9q)**
  - idic(X)(q13)

- **Balanced abnormalities**
  - t(11;16)(q23.3;p13.3)
  - t(3;21)(q26.2;q22.1)
  - t(1;3)(p36.3;q21.1.2)
  - t(2;11)(p21;q23.3)
  - t(5;12)(q32;p13.2)
  - t(5;7)(q32;q11.2)
  - t(5;17)(q32;p13.2)
  - t(5;10)(q32;q21)
  - t(3;5)(q25.3;q35.1)

* >3 abnormalities
** mutation of NPM1 or CEBPA trumps this abnormality
Proposed WHO Revisions for AML

• Revise criteria for AML with myelodysplasia-related changes
  – Remove de novo cases with no MDS-related cytogenetic abnormalities if $NPM1$ or $CEBPA^{dm}$ mutated
  – Revise MDS-related cytogenetic abnormalities

• Add section on familial myeloid neoplasms
Algorithmic Approach

Morphologic Review

>20% Blood or Marrow Blasts

<20% Blood or Marrow Blasts
Algorithmic Approach

- **<20% Blood or Marrow Blasts**
  - **Cytogenetics**
    - t(8;21), inv(16), t(16;16) or *PML-RARA*
    - t(5;14)
    - Normal or other abnormalities

- **AML with recurrent genetic abnormality**
- **ALL with t(5;14)**
- **Not acute leukemia**
Algorithmic Approach

- >20% Blood or Marrow Blasts
- Immunophenotype
  - Ambiguous
  - Myeloid
  - Precursor B
  - Precursor T
  - AUL
  - MPAL
  - ETP-LB
  - T-LB
Algorithmic Approach (2008)

History and Genetics

Therapy-related AML

- Hx of cytotoxic therapy
- Recurrent genetic abnormality
- Prior MDS or MDS-related cytogenetics
- Down syndrome

Myeloid proliferation of Down Syndrome

AML with recurrent genetic abnormality

- NPM1 or CEBPA mutated

AML, not otherwise specified

Morphology for multi-lineage dysplasia

- Present
- Absent

AML with myelodysplasia-related changes

- None

Myeloid
Algorithmic Approach (Proposed)

Myeloid

History and Genetics

Mutation Studies

- NPM1, CEBPA\textsuperscript{dm} mutated
- RUNX1 mutated

Therapy-related AML

Myeloid proliferation of Down Syndrome

AML with myelodysplasia-related changes

- Present
- Absent

AML with recurrent genetic abnormality

AML, not otherwise specified
AML Mutation Studies
(FLT3, NPM1, CEPBA, KIT, RUNX1, DNMT3A, TET2, IDH1/2, ASXL1, WT1 ....)

Mutated NPM1 or CEBPA$^{dm}$

History of Prior Therapy

History of MDS or MDS/MPN

MDS-related CG abnormality other than del(9q)

AML with MDS-related changes

None

Other recurring CG abnormality

AML with recurrent genetic abnormality

Therapy-related AML

AML with mutated NPM1 or AML with biallelic CEPBA mutation
AML Mutation Studies
(FLT3, NPM1, CEPBA, KIT, RUNX1, DNMT3A, TET2, IDH1/2, ASXL1, WT1 ....)

Mutated RUNX1

- History of Prior Therapy
- History of MDS or MDS/MPN
- MDS-related CG abnormality

- Therapy-related AML
- AML with MDS-related changes
- AML with recurrent genetic abnormality

- None
- Other recurring CG abnormality
- AML with mutated RUNX1

AML with MDS-related changes
AML Mutation Studies
(FLT3, NPM1, CEPBA, KIT, RUNX1, DNMT3A, TET2, IDH1/2, ASXL1, WT1 ....)

Other mutations

Note prognostic impact, but findings do not impact classification
WHO Revisions Summary

• Few major changes
• Attempt to update the 2008 classification based on newer data
  – Addition of disease specific mutations to diagnostic criteria (i.e. \textit{CSF3R} in CNL)
  – Reduced significance of multilineage dysplasia in AML in the setting of specific mutations
• Change to the general names to MDS groups
• Impact of \textit{SF3B1} on RARS
• Return of a category of MDS with MLD and ring sideroblasts
• Move of acute erythroleukemia (erythroid/myeloid type) to MDS
• Attempt to recognize the importance of mutation studies without making the classification overly complex
• Address familial myeloid neoplasms
  – Recognition may have largest impact
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