WHO Update: Acute Leukemias

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Disclosures

• None
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) (RBMI1-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 monocyctic 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(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)
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  - 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) (RBMY15-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
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- 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)
  - B-lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B-lymphoblastic leukemia/lymphoma with hypodiploidy
- T-lymphoblastic leukemia/lymphoma
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**

- 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
  - May show increased expression of CRLF2 by flow cytometry analysis
  - Some have activating mutations or rearrangements of genes, such as ABL1, JAK2, PDGFRB, CRLF2, EPOR, and/or of IKZF1 deletions/mutations
  - 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 4-5 or more copies of RUNX1 on a single cell
- 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
Probable 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 with mutated NPM1

AML with mutated CEBPA

2001

AML, Not Otherwise Categorized

AML, Not Otherwise Specified

History and/or cytogenetics

NPM1 and CEBPA

2008

Product-Limit Survival Function Estimates

Logrank p<0.0001

AML-NOS (n=38)
AML-MRC (n=44)

Progression Free Survival (days)
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?

proliferation and/or survival advantage; not affecting differentiation

AML

impaired hematopoietic differentiation and subsequent apoptosis
Mutations in AML

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*\(^{dm}\)) 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)

![Survival curves](image)

- **A** Mutated *NPM1*
  - Multilineage dysplasia
  - No multilineage dysplasia
  - $P = .97$

- **B** Wild-type *NPM1*
  - No multilineage dysplasia
  - Multilineage dysplasia
  - $P = .012$


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AML with mutated *NPM1* and an abnormal karyotype

- Abnormal karyotype identified in 14.7% of *NPM1* mutated AML cases
- +8, +4, -Y, del(9q) and +21 most frequent
- del(9q) is currently considered an MDS-related cytogenetic abnormality, but it appears to be unusually common in *NPM1* mutated cases
- Not clear if del(9q) has prognostic significance in this setting

AML with mutated *RUNX1*

- Gene located at 21q22
- Encodes the alpha subunit of the core binding factor
- Mutation in 12.5-13.2% of AML
- More frequent in older male patients
- Frequent prior history of MDS, or prior exposure to radiation
- Immature morphology and phenotype
- Frequent associated *MLL-PTD* or *ASXL1* mutations
- Rare *CEBPA* or *NPM1* mutations
- Poor response to therapy with shortened survival

AML with *BCR-ABL1*

- Difficult to distinguish from myeloid blast crisis of chronic myelogenous leukemia
- Deletion of antigen receptors, particularly *IGH*, recently shown to be specific for de novo disease
- Subset of cases have mutated *NPM1*
- Important to recognize due to presence of targeted (TKI) therapy

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

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 being discussed
  – AML with BCR-ABL1
    • Antigen receptor deletion
  – Refine APL with PML-RARA fusion
Proposed WHO Revisions for AML

• New and revised mutation subgroups
  – AML with \textit{RUNX1} mutation
    • 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 *RUNX1* mutation
  - AML with *CEBPA* mutation will have to be heterozygous/double mutation
  - *NPM1* and *CEBPA*\(^{\text{dm}}\) 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 $CEBPA^{dm}$ mutated
  - Revise MDS-related cytogenetic abnormalities
    - Allow del(9q) only in the absence of $NPM1$ mutation
MDS-related cytogenetic abnormalities

- **Complex karyotype***
- **Unbalanced abnormalities**
  - -7/del(7q)
  - -5/del(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;p13.3)
  - t(3;21)(q26.2;q22.1)
  - t(1;3)(p36.3;q21.1)
  - t(2;11)(p21;q23)
  - t(5;12)(q33;p12)
  - t(5;7)(q33;q11.2)
  - t(5;17)(q33;p13)
  - t(5;10)(q33;q21)
  - t(3;5)(q25;q34)

*≥3 abnormalities
** mutation of *NPM1* 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

Immunophenotype

Ambiguous
- AUL
- MPAL

Myeloid

Precursor B

Precursor T
- ETP-LB
- T-LB
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 (2008)

Myeloid

History and Genetics

Therapy-related AML

- Hx of cytotoxic therapy
- Down syndrome
- NPM1 or CEBPA mutated

AML with recurrent genetic abnormality

- Prior MDS or MDS-related cytogenetics
- Recurrent genetic abnormality

Morphology for multi-lineage dysplasia

- Present
- Absent

AML with myelodysplasia-related changes

- None

AML, not otherwise specified

Myeloid proliferation of Down Syndrome

AML, not otherwise specified
Algorithmic Approach (Proposed)

Myeloid

History and Genetics

- Therapy-related AML
- Myeloid proliferation of Down Syndrome

Mutation Studies

- AML with myelodysplasia-related changes
  - Present
  - Absent

- AML with recurrent genetic abnormality

Morphology for multi-lineage dysplasia

- NPM1, CEBPAdm, RUNX1 mutated

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

Mutated NPM1

- History of Prior Therapy
- History of MDS or MDS/MPN
- MDS-related CG abnormality other than del(9q)
- AML with mutated NPM1
- Therapy-related AML
- AML with MDS-related changes
- Other recurring CG abnormality
- AML with recurrent genetic abnormality
AML Mutation Studies
(FLT3, NPM1, CEPBA, KIT, RUNX1, DNMT3A, TET2, IDH1/2, ASXL1, WT1...)

Mutated RUNX1

History of Prior Therapy

Therapy-related AML

History of MDS or MDS/MPN

AML with MDS-related changes

MDS-related CG abnormality

None

Other recurring CG abnormality

AML with recurrent genetic abnormality

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

Mutated CEBPA

History of Prior Therapy

History of MDS or MDS/MPN

Therapy-related AML

AML with MDS-related changes

AML with MDS-related changes

AML, NOS

AML with recurrent genetic abnormality

Homozygous mutation?

Yes

No

None

Other recurring CG abnormality

AML with mutated CEBPA

None
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
Acute Leukemia Summary

• Few major changes
• Attempt to update the 2008 classification based on newer data
  – Reduced significance of multilineage dysplasia in the setting of specific mutations
• 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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Questions?