SH/EAHP 2017 Session 3: Genetic Testing in Diagnosis of Acute Leukemias: Introduction

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Classification of acute leukemias has become increasingly complex

- French-American-British classification of 1976
  - Morphology
  - Cytochemistry
- WHO classifications of 2001 and 2008
  - Morphology
  - Clinical features
  - Immunophenotype
  - Genetics
- 2016 revision of WHO classification
  - Includes substantial new genetic knowledge

2016 WHO classification of AML

25 subtypes

- 11 subtypes include specific genetic alterations
  - Including 2 new provisional subtypes
    - AML with mutated RUNX1
    - AML with BCR-ABL1
- Incorporation of refined molecular understanding in existing subtypes

Myeloid neoplasms with germ line predisposition

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Arber et al., Blood, 2016

2016 WHO classification of ALL

13 subtypes of lymphoblastic leukemia, including

- 9 subtypes with specific genetic alterations
  - 2 new provisional subtypes of B-ALL
    - B-ALL, BCR-ABL1-like
    - B-ALL with iAMP21
  - 1 new provisional subtype of T-ALL
    - Early T-cell precursor lymphoblastic leukemia
  - New provisional entity of NK cell lymphoblastic leukemia
- Incorporation of refined molecular understanding in existing subtypes

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Arber et al., Blood, 2016

Why is systemic classification important?

Clinical practice

- Correct diagnosis, universally understood
- Refined prognosis, including risk stratified treatment plans
- Best therapy, including targeted agents

Advancing the field

- Universal system of classification allows for widest applicability of clinical research findings

Types of genetic aberration

Chromosomal rearrangements

Segmental or whole chromosome gains and losses

Focal copy number alterations, particularly amplification

Sequence alterations, including single nucleotide variants (SNVs) and small indels

Techniques

Karyotype

FISH

PCR

RT-PCR

Microarray

Sanger sequencing

Next-generation sequencing (NGS) of DNA (sequence variants, copy number, translocations)

NGS of RNA (expression patterns, translocations)

Which test(s) to use?

2017 guidelines for diagnostic testing

- College of American Pathologists and the American Society of Hematology (diagnostic testing in acute leukemia)

and

- European LeukemiaNet (adult AML)

CAP-ASH guidelines

ALL

- Karyotype
- Pediatric B-ALL, testing for:
  - t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
  - t(9;22)(q34.1;q11.2); *BCR-ABL1*
  - *KMT2A* (*MLL*) translocation
  - iAMP21
  - trisomy 4 and 10
- Adult B-ALL: testing for:
  - t(9;22)(q34.1;q11.2); *BCR-ABL1*
  - *KMT2A* (*MLL*) translocation testing may also be performed
- May also perform other mutational analysis that includes, but is not limited to
  - B-ALL: *PAX5*, *JAK1*, *JAK2*, *IKZF1*, and/or overexpression of CRLF2
  - T-ALL: *NOTCH1* and/or *FBXW7*

AML (similar to ELN recommendations)

- Karyotype
- All or most AML:
  - *FLT3*, *NPM1*, *CEBPA*, and *RUNX1*
  - May also perform other mutational analysis that includes, but is not limited to, *IDH1*, *IDH2*, *TET2*, *WT1*, *DNMT3A*, and/or *TP53*. *ASXL1* (ELN risk group)
- Core binding factor AML: *KIT*
- Suspected APL: rapid assessment of *PML-RARA*

MPAL

- t(9;22)(q34.1;q11.2); *BCR-ABL1*, and *KMT2A* (*MLL*) translocations

CAP-ASH: Arber et al., Arch Pathol and Lab Med, 2017; ELN: Dohner et al., Blood 2017

Diagnostic challenges

Variation from established diagnostic category

Co-existing alterations and/or diagnoses

Unusual clinical context

BCR-ABL1-like B-ALL

Findings of new, recurrent molecular genetic alterations and new targeted therapies

Genetic testing in diagnosis of acute leukemias: Session 3 oral presentations

Case #	Contributor	Panel Diagnosis	
SH2017-0180	C.C. Yin/K. Patel MD Anderson Cancer Center	APL with variant *RARA* rearrangement (*IRF2BP2-RARA*)	
SH2017-0281	D. Yang/J. Bauer University of Wisconsin	AML with mutated *RUNX1*	Other co-mutations
SH2017-0299	A. Vogel Thomas Jefferson University	AML with *BCR-ABL1*	
SH2017-0328	K. Holder University of Texas Health San Antonio	Therapy-related myeloid neoplasm (AML) with t(9;11)	Post therapy for APL
SH2017-0108	E. Mason Vanderbilt University Medical Center	LPL in setting of B-ALL	*KMT2A* rearrangement
SH2017-0366	M. Harris Boston Children's Hospital	B-ALL with iAMP 21	
SH2017-0343	S. Ondrejka Cleveland Clinic	B-ALL, *BCR-ABL1*-like	*PDGFRB* rearrangement