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

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

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

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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

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