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What is New in the 5th Edition of the World Health Organization Classification of Acute Myeloid Leukemia

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Abstract

Recent advancements in the clinical significance of inherited predisposition to acute myeloid leukemia (AML), the diagnostic and prognostic value of genomic abnormalities, quantitative assessment of measurable residual disease (MRD), the utility of MRD in assessing disease risk and therapeutic response, the development of novel therapeutic agents, as well as the developments in allogeneic hematopoietic cell transplantation make change in AML classification, diagnostic and prognostic algorithms, and therapeutic practices is warranted.

Abbreviations: WHO: World Health Organization; AML: Acute Myeloid Leukemia; biCEBPA: Biallelic CEBPA; bZIP: basic Leucine Zipper; smbZIP-CEBPA: single mutations located in the bZIP region of the CEBPA gene; AML-pCT: AML Post Cytotoxic Therapy; AML-MR: AML myelodysplasia-related; ALAL: Acute Leukemias of Ambiguous lineage

Introduction

The third, fourth and revised fourth editions of the World Health Organization (WHO) classification of the tumors of hematopoietic and lymphoid tissues were done by collaborations between the WHO, the Society for Hematopathology (SH), and the European Association for Haematopathology (EAHP). Major advances in the understanding of acute myeloid leukemia (AML) have occurred since the publication of the fourth edition of WHO classification in 2008. The revised fourth edition of WHO classification was tasked to be an update of this version based on new knowledge in AML. A more significant change in disease classification is warranted. The fifth edition of WHO Classification as planned by the International Agency for Research on Cancer (IARC) lacked oversight of SH and EAHP and did not follow the clinical advisory committees (CAC) process [1]. AML is classified by WHO classification into two families: AML with defining genetic abnormalities and AML defined by differentiation [2].

AML with defining Genetic Abnormalities (2)

Key changes

i. Most AML of this type require less than 20% blasts for diagnosis. The only exception is AML with CEBPA mutation and AML with BCR: ABL1 which still require at least 20% blasts for diagnosis. This blast cutoff of the former is needed to avoid overlap with myeloid blast phase of CML.

ii. The definition of AML with CEBPA mutation is now includes biallelic (biCEBPA) and single mutation located in the basic leucine zipper (bZIP) region of the CEBPA gene (smbZIP-CEBPA).

iii. Three AML types with characteristic rearrangements involving KMT2A, MECOM, and NUP98 are recognized. AML with KMT2A rearrangement replaces "AML with t(9;11)(p22;q23).

iv. AML with rare fusions that may be defined in future editions of the classification are incorporated under AML with other defined genetic alterations.

v. AML, NOS is no longer applicable.

vi. AML with somatic RUNX1 mutation is not recognized as a distinct type due to lack of sufficient unifying characteristics.

vii. **The term AML, myelodysplasia-related (AML-MR)** has replaced the previous term AML "with myelodysplasia-related changes". MDS, arising de novo or following a history of MDS or

MDS/MPN is kept under AML-MR. This AML type requires presence of ≥20% blasts expressing a myeloid immunophenotype and harboring specific cytogenetic and molecular abnormalities. The defining cytogenetic criteria are complex karyotype (≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities), 5q deletion or loss of 5q due to unbalanced translocation, monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation, 11q deletion, 12p deletion or loss of 12p due to unbalanced translocation, monosomy 13 or 13q deletion, 17p deletion or loss of 17p due to unbalanced translocation, and isochromosome 17q idic(X)(q13). The defining somatic mutations are SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, and STAG2. > 95% of these mutations are present specifically in AML post MDS or MDS/MPN. The presences of one or more of the previously mentioned cytogenetic or molecular abnormalities and/or history of MDS or MDS/MPN are required for AML-MR diagnosis. Morphology alone is not sufficient to make AML-MR diagnosis.

AML defined by differentiation [2]

This type lacks defining genetic abnormalities. Recently, a BCL11B rearrangement is identified in a subset of AML with minimal differentiation.

Secondary myeloid neoplasms [2]

This new segregated category includes diseases arising in the setting of certain predisposing factors such as exposure to cytotoxic therapy or germline predisposition. These predisposing features are appended as disease attributes that should be added as qualifiers of disease entities primarily defined by genetic abnormalities e.g. AML with KMT2A rearrangement post cytotoxic therapy.

AML post cytotoxic therapy (AML-pCT)

This term now replaces therapy related [3]. The majority of AML-pCT is associated with TP53 mutations. The outcomes of patients with biallelic (multi-hit) TP53 alterations are generally worse [2].

Myeloid neoplasms with germline predisposition

The clinical manifestations of these diseases are grouped into three subtypes: germline disorders associated with preexisting platelet defects (quantitative and qualitative), germline disorders associated with potential other organ dysfunction and germline disorders without preexisting platelet defects or potential other organ dysfunction [2]. Some disorders are associated with myeloid malignancies only (e.g., CEBPA), whereas others confer risk to a variety of hematopoietic malignancies and solid tumors [3]. Lymphoid neoplasms can also occur [2].

Consider clinical testing for a germline predisposition allele(s) in the following [3]

i. Personal history of ≥2 cancers, 1 of which is a hematopoietic malignancy (order does not matter).

ii. Personal history of a hematopoietic malignancy plus: another relative within two generations with another hematopoietic malignancy, or other hematopoietic abnormalities or a solid tumor diagnosed at age 50 or younger.

iii. Presence of a deleterious gene variant (e.g., CHEK2 I200T and truncating DDX41 variants) in tumor profiling that could be a germline allele, especially if it is present during remission.

iv. Diagnosis of hematopoietic malignancy at an earlier age than average (e.g., MDS diagnosed ≤ 40 y).

Caution in the following situations [3]

i. Confirm the status of germline variant by its presence in DNA derived from a tissue source not likely to undergo somatic mutation frequently (e.g., cultured skin fibroblasts or hair follicles).

ii. Interpreting data from tumor-based panels cautiously because hematopoietic tissues frequently undergo somatic reversion leading to false-negative results.

iii. Use of hematopoietic donor stem cells from carriers of deleterious RUNX1 and CEBPA variants is prohibited.

Acute leukemias of mixed or ambiguous lineage (ALAL)

ALAL are arranged into two families: ALAL with defining genetic abnormalities and ALAL, immunophenotypically defined. Two new subtypes of ALAL with defining genetic alterations are added. The first subtype is MPAL with ZNF384 rearrangement, which is commonly, has a B/myeloid immunophenotype and is identified in ~50% of pediatric B/myeloid MPAL. The other subtype is ALAL with BCL11B rearrangement, identified in ~20-30% of T/myeloid MPAL [2].

Conclusion

Based on these changes, AML classification is updated to include morphologic, genetic and clinical new data.

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