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Classification of Myelodysplastic Neoplasms in the 5th Edition Of the World Health Organization Classification Compared to 2022- International Consensus Classification

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Abstract

In 2022, the fifth edition of the World Health Organization (WHO) classification (WHO-2022) emphasized the integration of clinical, molecular, and pathologic parameters into myelodysplastic neoplasms (MDS) diagnosis. Additionally, the 2022- International Consensus Classification (ICC) recategorized myeloid neoplasms based on the introduction of new entities and on refining the criteria of the existing diagnostic categories. The following editorial will stress, on illustrating the differences between MDS classification in 2022- ICC, compared to the 2022 fifth edition of WHO classification.

Abbreviations: MDS: Myelodysplastic neoplasms; WHO: World Health Organization; HSC: Hematopoietic stem cell; ICC: International Consensus Classification, NOS: Not otherwise specified.

Introduction

Myelodysplastic neoplasms (MDS) are clonal hematopoietic neoplasm characterized by combination of unexplained persistent cytopenia(s), presence of morphologic dysplasia and a propensity to progress to bone marrow failure or acute myeloid leukemia. In general, the blood count abnormality in MDS is chronic in duration (typically 4 months or even longer) and is not explained by a drug, toxin, or any comorbid condition [1].

MDS starts with somatic mutations in the genome of the disease-initiating multipotent hematopoietic stem cell (HSC). These mutations provide growth and survival advantage at the level of the HSC and enhance the self-renewal and the accumulation of clonal hematopoiesis over time, resulting in abnormal progenitor and precursor cells [2]. The most common alterations at the onset of MDS include recurrent somatic mutations in the function of the splicing factors (SF3B1, SRSF2, ZRSR223, and U2AF1) and the DNA methylation and chromatin modifiers (DNMT3A, TET2, and ASXL1). Frequent cytogenetic alterations include partial deletion of chromosomes 5 (5q) and 20 (20q) or the complete loss of chromosome 7 (monosomy 7) or partial deletion of the long arm of chromosome 7. MDS onset can be accelerated by cytotoxic chemotherapy, transplantation after other cancers, the presence of germline predisposition mutations, for e.g., those affecting telomere maintenance genes, the DEAD box protein member (DDX41), the GATA2 transcriptional factor, or any type of stress (e.g., inflammation) which confers a fitness advantage to the mutant clone [3].

What is new in the MDS classification in the 5th edition of the World Health Organization (WHO) classification

New terminology

The term myelodysplastic neoplasms (abbreviated MDS) have replaced the previous term myelodysplastic syndromes in the 5th edition of the World Health Organization classification [4].

Updated and defining features of MDS in the 5th edition of WHO classification.

The recommended threshold for dysplasia is still set at 10% for any hematopoietic lineage as in the prior edition. MDS entities are now grouped into those having defining genetic abnormalities and those that are morphologically defined [4]. MDS, unclassifiable, which was present in the previous edition, is removed. The incorporation of clonal cytopenia of undetermined significance (CCUS) in the updated WHO classification of MDS

classification obviates the need for MDS "unclassifiable" (MDS-U) or "NOS" attributes [4].

MDS has been classified into [4]

i. Myelodysplastic neoplasms with defining genetic abnormalities:

MDS with low blasts and isolated 5q deletion (MDS-5q)

MDS with low blasts and SF3B1 mutation (MDS-SF3B1)

MDS with biallelic TP53 inactivation (MDS-biTP53)

ii. MDS, morphologically defined

MDS with low blasts (MDS-LB)

MDS, hypoplastic (MDS-h) (cellularity of bone marrow is less than 20%)

MDS with increased blasts (MDS-IB)

a. MDS-IB1 (5–9% bone marrow blasts or 2–4% peripheral blood blasts)

b. MDS-IB2 (10-19% bone marrow blasts or 5–19% peripheral blood blasts or Auer rods)

c. MDS with fibrosis (MDS-f) (5–19% bone marrow blasts; 2–19% peripheral blood blasts)

What is new in the MDS classification in the 2022 - International Consensus Classification (ICC)

The 2022-ICC for myeloid neoplasms has placed MDS in a broader group of clonal cytopenias that include clonal cytopenia of undetermined significance (CCUS) and other related entities. In the 2022-ICC diagnosis MDS requires presence of blast count less than 10% in the bone marrow or peripheral blood. Morphologic dysplasia remains the main feature that defines MDS. Some of the cases categorized as MDS based on cytogenetic abnormalities are now classified as CCUS [5].

Two new genetically defined categories have been introduced in the 2022- ICC for MDS: MDS with SF3B1 mutation (MDS-SF3B1) and MDS with mutated TP53. MDS-SF3B1 has replaced the prior entity of MDS with ring sideroblasts (MDS-RS). MDS with mutated TP53 is defined by the presence of multi-hit TP53 mutation [5]. Multi-hit TP53 mutation is defined as i. single TP53 mutation with variant allele frequency (VAF) > 50%, or ii. presence of two distinct TP53 mutations, each with VAF ≥ 10% or iii. a single TP53 mutation with VAF ≥ 10% associated with 17p13.1 deletion, complex karyotype, or copy neutral loss of heterozygosity at the 17p TP53 locus, confirmed by conventional karyotype, fluorescence in situ hybridization, or molecular genetic copy number analysis [6].

The name MDS with del(5q) have been introduced in the 2022 -ICC to replace the name MDS with isolated del(5q) which was present in the revised fourth edition of WHO classification. No further other changes were present in MDS with del(5q). The prior category of MDS "unclassifiable" (MDS-U) has been eliminated [6]. These 2022- ICC changes in MDS classification scheme as a whole resulted in an overall simplification of MDS classification from 8 separate entities in the revised 4th edition of WHO classification to 7 separate entities in the 2022- ICC [5].

Updated and defining features of MDS in the 2022-ICC [6]

i. MDS with mutated TP53

ii. MDS with excess blasts (MDS-EB) [(5%–9% bone marrow blasts or 2%–9% peripheral blood blasts)]

iii. MDS without excess blasts (MDS-EB) [(<5% bone marrow blasts or <2% peripheral blood blasts)]

a. MDS with mutated SF3B1 (MDS-SF3B1)

b. MDS with del(5q) [(MDS-del5q)]

c. MDS, NOS with single lineage dysplasia

d. MDS, NOS with multilineage dysplasia

e. MDS, NOS without dysplasia

The new categories "MDS/AML and "MDS/ AML with mutated TP53"

The 2022-ICC has introduced a new category "MDS/AML which is defined by the presence of 10%– 19% blasts in the bone marrow or peripheral blood, in the absence of recurrent genetic abnormalities defining AML (56). The 2022-ICC has recognized several cytogenetic and molecular abnormalities that reclassify some cases of MDS with excess blasts as AML [5]. MDS with excess blasts 2 (MDS-EB2) defined by WHO 2016/17 is now included in "MDS/AML category in the 2022- ICC and is no longer recognized as such in adult patients [6]. The presence of 10%–19% bone marrow blasts, in the context of TP53 mutated myeloid neoplasms, is noted as "MDS/ AML with mutated TP53" except in the setting of MDS/MPN or MPN. In contrast to MDS, a diagnosis of "MDS/ AML with mutated TP53" does not mandate the presence of multi-hit TP53 mutation [6].

Introduction of the concept of "diagnostic qualifiers"

The 2022-ICC has introduced the concept of "diagnostic qualifiers" such as history of chemotherapy/radiotherapy or underlying germline genetic predisposition for MDS or MDS/ AML subcategory. The qualifying statement entered after the morphologic/genetic diagnosis, instead of a separate subcategory (e.g., therapy related" rather than "therapy-related MDS") [6].

Conclusion

Both the fifth edition of WHO classification (WHO-2022) and the 2022 -International Consensus Classification (ICC) emphasize the integration of clinical, molecular/ genetic, morphologic and

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immunophenotypic parameters for more precise diagnosis, prognosis and improved treatment outcome of hematopoietic neoplasms.

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