Guideline Interpretation

The 2016 revision to the World Health Organization classification of myelodysplastic syndromes

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Myelodysplastic syndromes (MDS) are a group of diverse clonal hematopoietic disorders characterized by ineffective hematopoiesis, manifested by morphologic dysplasia in hematopoietic cells and by bone marrow failure, refractory peripheral cytopenia(s) and by a risk of progression to acute myeloid leukemia (AML). The World Health Organization (WHO) Classification of MDS was last updated in 2008.[1,2] The recently identified molecular features by next generation sequencing (NGS) has provided novel insights for the understanding of pathobiology of MDS, and yielded new markers related with diagnosis and prognosis.[3-5] The clinical and pathological studies had validated the WHO postulate of an integrated approach, including hematologic, morphologic, cytogenetic and molecular genetic findings.[6] With the emergence of so much information and experience regarding MDS, a new revision of the criteria for MDS has become necessary. The new revised classification introduced refinements in the cytopenia and morphological changes, and also the influence of genetic information in MDS diagnosis and classification.

Cytopenia is a "sine qua non" for the diagnosis of MDS. Although the lowering of neutropenia prognostic threshold in IPSS-R to 0.8 × 10^9/L,[7] the WHO thresholds defining cytopenia still remain as in the original IPSS: hemoglobin <10g/dL, platelets <100× 10^9/L, absolute neutrophil count <1.8× 10^9/L.[8] The classification considers blood and bone marrow blast proportion, which myeloid cell lineages exhibit dysplastic changes greater than 10% of cells morphologically, whether the ring sideroblast erythroid precursors or Auer rods are present or not and, to a limited extent, karyotype and molecular genetic findings. The degree and not the lineages of cytopenia impacts the MDS prognosis, and in MDS, the lineage(s) manifesting morphological dysplasia frequently do not correlate with the specific cytopenia(s).[9-11] So, the terms such as "refractory anemia" and "refractory cytopenia" are removed and replaced with "myelodysplastic syndrome", which means that the diagnosis of MDS needs be determined firstly, and then the classifications needs to be done.[6] The new terms for each subtypes of adult MDS are MDS followed by: single versus multilineage dysplasia, ring sideroblasts, excess blasts, or the del(5q) cytogenetic abnormality (Table 1 and Table 2). In childhood MDS, refractory cytopenia of childhood remains a provisional term in the category of MDS.

The thresholds defining dysplasia remain as 10% dysplastic cells in myeloid lineages. Commonly observed dysplastic features include megaloblastoid erythroid maturation, erythroid precursor with nucleation abnormalities, or ring sideroblasts, neutrophil hypolobulation or hypogranulation, and small megakaryocytes. It is difficult but necessary to separate reactive causes of cytopenia and dysplasia from MDS, prior to making a diagnosis and classification of MDS, particularly when the dysplasia is subtle and limited to one lineage, especially in erythroid lineage. By immunostaining for megakaryocyte markers in the BM trephine, the presence of small megakaryocytes is relatively specific for myelodysplasia and

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Table 1: 2016 WHO Criteria of classifications of myelodysplastic syndromes

Type	Dysplastic lineages	Cytopenias[1]	Ring sideroblasts in erythroid elements of BM	Blasts	Cytogenetics
MDS-SLD	1	1 or 2	RS < 15% (or < 5%[2])	PB < 1% BM < 5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-MLD	2 or 3	1-3	RS < 15% (or < 5%[2])	PB < 1% BM < 5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-RS MDS-RS-SLD	1	1 or 2	RS ≧ 15% (or ≧ 5%[2])	PB < 1% BM < 5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-RS-MLD	2 or 3	1-3	RS ≧ 15% (or ≧ 5%[2])	PB < 1% BM < 5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	PB < 1% BM < 5% No Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS-EB MDS-EB-1	0-3	1-3	None or any	PB 2 ~ 4% or BM 5 ~ 9%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	PB 5 ~ 19% or BM 10% ~ 19% or Auer	Any
MDS-U With 1% PB blast	1-3	1-3	None or any	PB = 1%[3], BM < 5%, Auer rods	Any
with SLD and pancytopenia	1	3	None or any	PB < 1% BM < 5% No Auer rods	Any
Defining cytogenetic abnormality	0	1-3	< 15%[4]	PB < 1% BM < 5% No Auer rods	MDS defining abnormality
RCC	1-3	1-3	None	PB < 2% BM < 5% No Auer rods	Any

WHO: World Health Organization; MDS: myelodysplastic syndromes; PB: peripheral blood; BM: bone marrow; RS: ring sideroblasts; MDS-SLD: MDS with single lineage dysplasia; MDS-MLD: MDS with multilineage dysplasia; MDS-EB: MDS with excess blasts; MDS-U: MSD, unclassifiable; RCC: refractory cytopenia of childhood. [1]Cytopenias MDS-defining: Hb < 100g/L, PLT < 100×10^9/L, ANC < 1.8×10^9/L; absolute monocytes count < 1.0×10^9/L; [2]with *SF3B1* mutation; [3]1% PB blasts must be recorded on at least two separate observations; [4]If with ≥ 15% ring sideroblasts and significant erythroid dysplasia, and are classified as MDS-RS-SLD.

reproducible. For patients with excess blasts or typical cytogenetic changes of MDS, such as MDS with excess blasts-1, -2, or MDS, unclassifiable (MDS-U), the diagnosis of MDS can be made, although the dysplastic cells percentage does not reach the 10% threshold (Table 1). The cytogenetic findings and the myeloblast percentage have a significant and independent impact on the prognosis of MDS.

The myeloblast percentage is determined by counting the cellular BM aspirate smears and the peripheral blood smear. As the flow of cytometric enumeration of marrow blasts is subject to various technical artifacts, it should not replace a marrow aspirate manual differential count. The blast cells include myeloblasts, monoblasts and promonocytes, erythroblast and megakaryoblast. The promyelocyte is determined as blast only in acute promyelocytic leukemia. In the updated classification of myeloid neoplasms, the case previously diagnosed as erythroid/myeloid subtype of acute erythroid leukemia mostly refer to MDS with excess blasts, since the denominator used for calculating the blast

Table 2: Comparison between the editions 2008 and 2016 WHO classification of MDS

2008	2016
Refractory cytopenia with unilineage dysplasia (RCUD)	MDS with single lineage dysplasia (MDS-SLD)
Refractory anemia (RA)	
Refractory neutropenia (RN)	
Refractory thrombocytopenia (RT)	
Refractory anemia with ring sideroblasts (RARS)	MDS with ring sideroblasts (MDS-RS) MDS-RS-SLD MDS-RS-MLD
Refractory cytopenias with multilineage dysplasia	MDS with multilineage dysplasia (MDS-MLD)
Refractory anemia with excess blasts (RAEB)	MDS with excess blasts (MDS-EB)
RAEB-1	MDS-EB-1
RAEB-2	MDS-EB-2
MDS with isolated del(5q)	MDS with isolated del(5q)
MDS, unclassifiable (MDS-U)	MDS, unclassifiable (MDS-U)
Refractory cytopenia of childhood (provisional)	Refractory cytopenia of childhood (provisional)

WHO: world health organization; MDS: myelodysplastic syndromes.

percentage is all nucleated bone marrow cells, and not the "non-erythroid cells" even though the erythroid precursors exceed 50% of all BM cells.[6] The presence of 1% blasts in the PB, with <5% BM blasts, defines as MDS-U. Since 1% blasts may not be reproducible as a single observation, it must be recorded on at least two separate occasions. MDS-U also include cases with single lineage dysplasia or isolated del(5q) and pancytopenia, or defining cytogenetic abnormality and one to three lineages cytopenia.

The cytogenetic abnormalities listed are the same as in the 2008 WHO Classification. MDS can be defined in cytopenic patients when they are associated with MDS-defining cytogenetic abnormalities, unless that abnormality is +8, -Y, or del(20q).[1,2] -Y may be a phenomenon in males during physiological senescence, +8 and del(20q) could emerge in aplastic anemia, and the response to immunosuppressive therapy very well. Because of the heterogeneity of cytogenetic alterations in MDS, the abnormal chromosomes must be demonstrated by the routine 20 metaphase cytogenetic analysis, not by fluorescence in situ hybridization (FISH) or sequencing technologies.

MDS with isolated del(5q) remains as specific MDS subtype with only cytogenetic abnormality. As there is no adverse effect of one chromosomal abnormality in addition to the del(5q), the subtype of MDS with isolated del(5q), may also be diagnosed if there is one additional cytogenetic abnormality besides the del(5q), unless that abnormality is monosomy 7 or del(7q).[6] Cytogenetics is strongly correlated with not only the calculation prognosis but also selection of the most effective therapy; thus, a complete BM karyotype remains the standard work up evaluation procedure of the patient with MDS. Cytogenetic prognostic groups have been proposed in the revised international score (IPSS-R) scheme, which include 5 different subgroups including 20 different alterations (Table 3).[7]

Over the last years, a number of studies have been published describing the comprehensive analysis of incidence and the clinical impact of multiple recurring genetic mutations in myeloid neoplasms.[3-5] Targeted sequencing of a group of genes by NGS could detect mutations in 80-90% of MDS patient; the most commonly mutated genes in MDS are *SF3B1, TET2, SRSF2, ASXL1, RUNX1, TP53*, *U2AF1, DNMT3A,* and *EZH2*.[12-14] By whole-exome sequencing of DNA in the peripheral-blood cells, the acquired clonal mutations identical to those seen in myeloid tumor and MDS, can occur in apparently healthy individuals, so-called "clonal hematopoiesis of indeterminate potential" (CHIP).[15] And in patients with idiopathic cytopenias of

Table 3: Cytogenetic prognostic groups in the IPSS-R

Prognostic groups	Chromosomal categories	Median survival time (months)
Very good	del(11q), −Y	60.8
Good	Normal, del(5q), double aberrations including del(5q), del(12p), del(20q)	48.5
Intermediate	del(7q), +8, i(17q), +19, any other, independent clones	25.0
Poor	inv(3)/t(3q)/del(3q), −7, −7/7q, double aberrations including −7/7q−, complex karyotypes with 3 abnormalities	15.0
Very poor	Complex karyotypes with >3 abnormalities	5.7

IPSS-R: Revised International Prognostic Scoring System.

undetermined significance (ICUS), somatic mutations indicative of clonal hematopoiesis have also been identified. It will be referred to as clonal cytopenias of undetermined significance (CCUS).[16] The asymptomatic persons with CHIP are at an increased risk of developing a hematologic malignancy, particularly if the size of the detected clone is large. Whether the risks are higher in CCUS is unknown [16] Importantly, the natural history of CHIP and CCUS is not yet fully understood and appears to be highly variable, although some patients with CHIP subsequently develop MDS. Since no somatically mutated gene is unique to MDS, the presence of MDS-associated somatic mutations alone is not considered as a diagnostic of MDS in 2016 edition of WHO criteria, even in a patient with CCUS. Additional information is required to determine the prevalence, nature and risk of somatic mutations found in CCUS that do not meet the diagnostic criteria for MDS. Further studies are needed to investigate possible links between specific mutations, mutant allele fraction, or mutation combinations and subsequent development of MDS.

The spliceosome gene *SF3B1* is the frequently recurrent mutation in MDS, and which is associated with ring sideroblasts.[17] *SF3B1* mutation is an early event in MDS pathogenesis, with distinct gene expression profile, and predicts a favorable prognosis.[17,18] Since studies have shown that the actual percentage of ring sideroblasts does not impact the prognosis of MDS, the diagnosis of MDS with ring sideroblasts (MDS-RS) is identified when the ring sideroblasts comprise just 5% of the nucleated erythroid cells, if *SF3B1* mutation is presented.[6] Without *SF3B1* mutation, the threshold is still 15% of the ring sideroblasts of nucleated erythroid cells. In the revised classification, MDS-RS include cases with ring sideroblasts and multilineage dysplasia, lacking excess blasts or an isolated del(5q) abnormality, thus MDS-RS include MDS-RS with single lineage dysplasia (refractory anemia with ring sideroblasts previously) and cases with multilineage dysplasia (refractory cytopenia with multilineage dysplasia previously).[6] In MDS-RS, the influence of multilineage dysplasia versus single lineage dysplasia, and *SF3B1* mutation on prognosis is not identified. But MDS-RS without *SF3B1* mutation might be associated with an adverse prognosis as compared to those with the mutation.[6,18]

TP53 mutations are detected in approximately 5-20% of cases in MDS by NGS.[19-21] It is consistently shown that *TP53* mutations are associated with the higher-risk MDS, therapy-related MDS and MDS with complex cytogenetics. It is well understood that *TP53* mutational status predicts an aggressive disease in MDS and poor resistance to chemotherapy and allo-hematopoietic stem cells transplantation (allo-HSCT) in MDS and AML, lenalidomide in patients with del(5q) although del(5q) is generally is a favorable prognosis MDS entity.[5,14,19-22] While MDS patients with *TP53* mutations initially respond well to hypomethylating agents (HMAs), the duration of response is significantly shorter than wild type patients. Thus, the evaluation for *TP53* mutations is recommended in patients with MDS with isolated del(5q), complex cytogenetics, or who need to be treated with chemotherapy, HMAs and allo-HSCT.

Conflicts of Interest

The authors declare no conflict of interest.

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