Guidelines for Management of MDS

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MDS guidelines ver 1:2021

Introduction

The myelodysplastic syndromes (MDS) comprise a group of hematologic malignancies characterized by clonal hematopoiesis, one or more cytopenias (ie, anemia, neutropenia, and/or thrombocytopenia), and abnormal cellular maturation. MDS shares clinical and pathologic features with acute myeloid leukemia (AML), but MDS has a lower percentage of blasts in peripheral blood and bone marrow (by definition, <20 percent). Patients with MDS are at risk of symptomatic anemia, infection, bleeding, and transformation to AML, the incidence of which varies widely across MDS subtypes.

Diagnosis

The diagnosis of MDS is based on cytopenias, dysplasia, cytogenetic abnormalities. MDS is classified based on WHO 2016 classification system as below

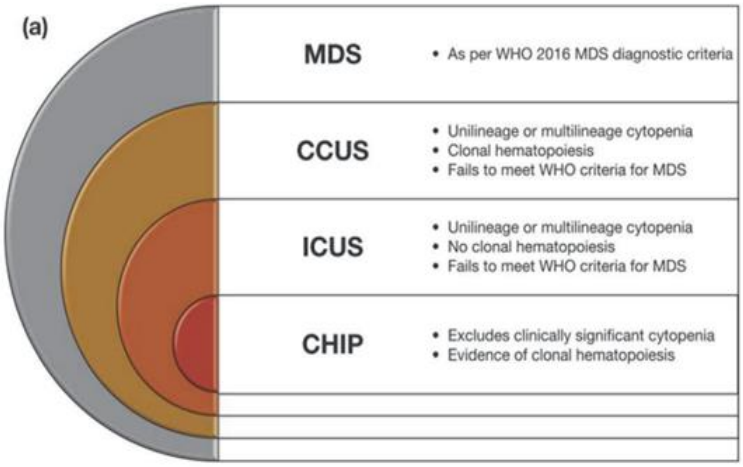
Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia	1	1 or 2	<15%/ <5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia	2 or 3	1-3	<15%/ <5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
MDS-U with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB 1%,‡ no Auer rods	Any
MDS-U with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
MDS-U based on defining cytogenetic abnormality		0	1-3	≥15%§	BM <5%, PB <1%, no Auer rods MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin <10 g/dL; platelet count <100 x10⁹/L; and absolute neutrophil count <1.8 x 10⁹/L. Rarely, myelodysplastic syndrome may present with mild anemia or thrombocytopenia above these levels. The peripheral blood monocyte count must be <1 x 10⁹/L. †If *SF3B1* mutation is present. ‡One percent peripheral blood blasts must be recorded on at least two separate occasions. §Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as myelodysplastic syndrome with ringed sideroblasts with single lineage dysplasia. BM: bone marrow; PB: peripheral blood.

Differential diagnosis

Differential diagnosis	Diagnostic tests
Aplastic anemia, pure red cell aplasia	Histology, cytology, parvovirus B19
Metastatic carcinoma	Histology, immunohistochemistry
Toxic bone marrow injury (alcohol, lead, zinc, copper deficiency, nonsteroidal anti-rheumatic drugs, etc.)	History, laboratory tests
Reactive bone marrow changes (infections e.g. sepsis, HIV, hepatitis, tuberculosis and other chronic infections, autoimmune diseases, thyroid disease, etc.), copper deficiency	Cytology, history, laboratory tests
Paroxysmal nocturnal hemoglobinuria	Immunophenotyping
Immune thrombocytopenia	History, course
Megaloblastic anemia	Vitamin B12/folic acid concentration
Hypersplenic syndromes	History/clinical features (splenomegaly)
Acute leukemia (especially erythroleukemia, FAB-M6)	Cytology, histology, immunophenotyping, genetic and molecular genetic testing
Myeloproliferative diseases (especially CMML, aCML, PMF)	Histology, cytogenetic and molecular genetic testing
Hairy cell leukemia, large granular lymphocytic leukemia	Cytology, immunophenotyping, molecular genetic testing (*BRAF*, *STAT3*), T-cell receptor
Congenital dyserythropoietic anemia (rare)	Molecular genetic testing
Idiopathic cytopenia of undetermined significance	ICUS minimal diagnostic criteria
Clonal cytopenia of undetermined significance	CCUS diagnostic criteria

HIV: human immunodeficiency virus; FAB: French-American-British; CMML: chronic myelomonocytic leukemia; aCML: atypical chronic myeloid leukemia; PMF: primary myelofibrosis; ICUS: idiopathic cytopenia of undetermined significance; CCUS: clonal cytopenia of undetermined significance.



Risk stratification is done as per IPSS and R-IPSS risk score

IPSS-R Scoring System

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good	-	Good	-	Intermediate	Poor	Very Poor
Blast %	≤2	-	>2 - <5		5-10	>10	-
Hb	≥100	-	80-<100	<80	-	-	-
Plt Count	≥100	50-<100	<50	-	-	-	-
Neut Count	≥0.8	<0.8	-	-	-	-	-

IPSS-R Cytogenetic Groups

Very Good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	Del(7q), +8, +19, i(17q), any other single or double indepdendent clones
Poor	-7, inv(3)/t(3q), double including -7/del(7q), complex w/ 3 abnormalities
Very Poor	Complex w/ >3 abdnormalities

IPSS-R Score vs Outcomes

Risk Category	Risk Score	Median Survival (yrs)	Median 25% AML transformation (yrs)
Very Low	≤1.5	8.8	-
Low	>1.5-3	5.3	10.8
Intermediate	>3-4.5	3.0	3.2
High	>4.5-6	1.6	1.4
Very High	>6	0.8	0.73

Investigations:

1. ***Baseline***
    a. Blood CP (with absolute counts)
    b. Peripheral film for differential count, manual platelet count and morphology
    c. Reticulocyte count
    d. Liver function tests
    e. Urea, creatinine
    f. HbsAg, Anti-HCV antibodies, HIV serology
    g. USG Abdomen
    h. X-ray Chest PA view
    i. Serum B12, folate
    j. Serum LDH, Uric acid
    k. C-reactive protein
2. ***To Confirm the diagnosis and exclude differential diagnosis***
    a. Bone marrow aspiration and trephine
    b. Cytogenetics
    c. Chromosomal breakage analysis (for patients <45 years)
    d. Immunophenotyping
    e. AML gene panel (for MDS cases with EB)
    f. PNH screening
    g. Other investigations to exclude DD as clinically indicated
3. ***For planning management***
    a. Serum erythropoietin levels
    b. FISH for del5q
    c. FISH for del17p
    d. Myeloid gene panel (if available by NGS) TP53 mutation, IDH1,IDH2, ASXL1
    e. Echocardiography

Management of MDS

1. ***Identify prognostic category***
    a. Low Risk MDS

i. R-IPSS ≤3
ii. IPSS ≤1

b. High Risk MDS
i. R-IPSS ≥3.5
ii. IPSS ≥1.5

2. ***Supportive care***
   a. ***Anemia:*** Red cell transfusion trigger needs to be individualized and targeted to relieve symptoms. Generally, transfuse if Hb< 8 g/dl and <9 g/dl in patients with ischemic heart disease
   b. ***Neutropenia and infection:***
      i. AFBMTC neutropenic fever guidelines for management of neutropenic fever
      ii. GCSF trial can be used in low risk patients with neutropenic fever
      iii. Mold active prophylaxis (Voriconazole/itraconazole) and anti-viral prophylaxis for patients with ANC < 0.1 x 10(9)/l or high fungal risk.
   c. ***Thrombocytopenia and bleeding:***
      i. No prophylactic platelet transfusion
      ii. Platelet transfusion only in case of clinically significant bleed or sepsis with PLT < 20 x 10(9)/l
      iii. No evidence to transfuse platelets with RCC transfusion
      iv. Antifibrinolytic agents for mucosal membrane bleeding reduces the need of platelet transfusion
      v. TPO agonists may be considered in cases with low risk MDS and severe thrombocytopenia with severe bleeding episodes ***(AFTER DEPARTMENTAL DISCUSSION)***

3. ***Low risk MDS***
   a. ***Anemia alone***

Table I. Validated model for predicting response to erythropoietin.[37]

Transfusion need	Point	S-EPO	Point
<2 units RBC/month	0	<500 u/l	0
≥2 units RBC/month	1	≥500 u/l	1

Predictive response to ESA: score 0 = 74%, score 1 point = 23%, score 2 points = 7%. ESA, erythropoietin-stimulating agent; RBC, red blood cells.

i. *RCC transfusion alone*: High NORDIC score and ineligible for HSCT and low intensity therapy
ii. *Erythropoiesis stimulating agents:*
    1. If NORDIC score 0, at least one transfusion per month and age <60 yrs
    2. Starting dose 20,000 units/week for 8 weeks and increase to maximum 30,000 /week for 8 weeks if no response.
iii. Lenalidomide: If del 5q positive and no response to ESA. Lenalidomide is contraindicated in bi/pan cytopenia.
iv. Iron chelation: for patients with ferritin >2000 pg/ml , age < 50 years, HSCT candidates . Deferasirox is recommended for iron chelation.

b. Thrombocytopenia

i. Observation
ii. TPO agonists trial of 3 months in selected cases if clinically significant bleeding and ineligible for HSCT ***(AFTER DEPARTMENTAL DISCUSSION)***

c. Hypoplastic MDS

i. Immunosupressive therapy with Cyclosporine if not eligible for HSCT.

d. Indications of Allo-HSCT (< 50 years old patients only)

i. Recurrent neutropenic sepsis (>2/year)
ii. High transfusion burden (>2 RCC /month)
iii. TP53 mutated
iv. Clinically significant recurrent bleeding
v. Fibrotic MDS with significant cytopenias (on case to case basis)

4. High Risk MDS

a. Transplant eligible

i. Age cut-off for HSCT 50 years
ii. Haplo-HSCT if age < 40 years
iii. **<10% blasts:** upfront HSCT without induction chemotherapy
iv. **>10% blasts:** HMA/LDAC +/- venetoclax for maximum 2 cycles followed by HSCT`

b. Transplant ineligible

i. Best supportive care

ii. Age <50 years: 2 cycles of HMA with Venetolax with ECOG 0-1 and absence of significant co-morbids . If achieves response, then complete 6 cycles otherwise supportive care only.

iii. Age> 50 years: Supportive care with or without LDAC.