Lower-Risk Myelodysplastic Syndromes: Putting Anemia Under the Spotlight

The publication of this infographic was funded by Bristol Myers Squibb.
Oncol AMJ. 2024;1[1]:44-45. https://doi.org/10.33590/oncolamj/WKMQ3310.
Date: 07/24
Job code: HE-US-2400517

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Epidemiology of MDS

MDS occurs predominantly in the aging population

~4.0 per 100,000
Overall age-adjusted incidence rate[1]

77 years
Median age at diagnosis[1]

Unmet needs in MDS

Up to 90% of patients may have anemia, leading to a significantly increased risk of mortality[2]

Transfusion burden is associated with a short OS[3]

Transfusion independence is associated with better QoL[3]

Symptoms of MDS

Typical presenting symptoms of MDS are generally non-specific and usually differ, depending on the type of cytopenia[4,5]

Most common symptoms of MDS		Other symptoms of MDS	
Anemia[4]		**Neutropenia[4]**	**Thrombocytopenia[4]**
Fatigue/weakness	Palpitations	Frequent infections	Easy bruising
Shortness of breath	Pale skin	Fever	Prolonged bleeding
Chest pains	Loss of appetite	Mouth sores	Petechiae
Headache	Cold extremities		

Diagnostic workup for MDS[9,10]

Diagnostic workflow	Diagnostic assessment
History and physical exam	Clinical suspicion of cytopenia
Peripheral blood count and peripheral blood smear	Clinical suspicion of cytopenia
Screening tests to rule out non-malignant causes **Anemia**: Exclude: GI bleeding, cardiac causes, inflammatory causes, and nutritional causes **Neutropenia**: Exclude: hypersplenism, autoimmune disorders, medication, toxic exposures **Thrombocytopenia**: Exclude: ITP, hypersplenism	Unexplained cytopenia
Specialist referral and additional tests to rule out other non-malignant or malignant causes • Bone marrow aspiration and biopsy • Somatic mutation analysis (gene sequencing) • Cytogenetics (karyotyping, FISH) • Immunophenatyping (flow cytometry)	MDS

MDS Diagnosis Algorithm

Diagnosis requires a combination of clinical suspicion, laboratory tests, hematologic and morphologic analysis, and cytogenetic and molecular evaluation[9,11,12]

Minimal prerequisites to establish MDS diagnosis:[4,11]
≥1 unexplained cytopenia
+
Exclusion of other potential disorders as primary reason for dysplasia/cytopenia

The diagnosis of MDS also requires ≥1 of the following:[4]

1. **≥10%** morphologic dysplasia (with or without an increase in blast cells) in ≥1 of the 3 lineages of hematopoietic cells
2. A blast cell count of **5-19%**
3. A specific MDS-associated karyotype, such as **del(5q), del(20q), +8, or −7/del(7q)**

Burden on Quality of Life Physical Problems

Physical problems

41% of patients with MDS reported moderate or severe mobility issues.[6] MDS causes a substantial and persistent functional decrement, partially due to fatigue[7]

Role functioning

36.1% of patients with MDS reported moderate or severe problems with usual activities (e.g., work, housework, or leisure activities).[6] The disease may affect employment, necessitating time off or compromising career opportunities[8]

Emotional problems

37.9% of patients with MDS reported moderate or severe issues with anxiety/depression.[6] Patients often find the emotional impact of MDS more problematic than the physical consequences.

Social functioning

34% of patients receiving blood transfusions felt they were burdening their family.[5] Transfusion requirements may disrupt routines and take time away from family and friends[8]

Classification[9,13-15]

Bone marrow blasts	WHO5	ICC
No dysplasia	CCUS	Clinical suspicion of cytopenia
<5%	MDS, hypoplastic MDS with LB MDS with LB and isolated 5q del MOS with LB and SF381 mutation*	Not included MDS-NOS with SLD, or with MLD MDS with del(5q) MDS with mutated SF387
5-9%	MDS with IB1 MDS with fibrosis	MDS with EB Not included
10-19%	MDS with IB2 MDS with biallelic *TP53* inactivation	MDS/AML MDS with mutated *TP53* MDS/AML with mutated *TP53*

Two updated classifications for MDS were developed in 2022: the WH05 and the ICC for Myeloid Neoplasms and Acute Leukaemia, which are overall similar, but with some differences in diagnostic criteria and nomenclatures.[9,13]

Risk stratification

The IPSS-R is the most commonly used risk stratification system in MDS, taking into account the degree of cytopenia, proportion of blasts in the bone marrow, and presence of cytogenetic abnormalities.[5,16,17]

Revised International Prognostic Scoring System (IPSS-R)[16]

Very Low	Low	Intermediate	High	Very High
19%	38%	20%	13%	10%

~77% of patients have LR-MDS[3]

Recently, the IPSS-M was developed, which integrated information from 31 gene mutations in addition to the IPSS-R components.[5,17,18]

Molecular International Prognostic Scoring System (IPSS-M)[18]

Very Low	Low	Moderate-Low	Moderate-High	High	Very High
14%	33%	11%	11%	14%	17%

Treatment goals for anemia in LR-MDS[5]

- Achieve RBC transfusion independence
- Improve hematological status
- Improve QoL
- Improve OS and delay AML transformation

Abbreviations: AML: acute myeloid leukemia; CCUS: clonal cytopenia of undetermined significance; del: deletion; EB: excess blasts; FISH: fluorescence in situ hybridisation; GI: gastrointestinal; IB: increased blasts; ICC: International Consensus Classification; IPSS-M: Molecular International Prognostic Scoring System; IPSS-R: Revised International Prognostic Scoring System; ITP: idiopathic thrombocytopenic purpura; LB: low blasts; LR: lower-risk; MDS: myelodysplastic syndromes; MLD: multilineage dysplasia; NOS: not otherwise specified; OS: overall survival; QoL: quality of life; RBC: red blood cell; SLD: single-lineage dysplasia; WHO: World Health Organization.

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