The 2013 Belgian Hematological Society recommendations for the diagnosis and classification of myelodysplastic syndromes

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The Belgian Hematological Society working group on myelodysplastic syndromes published their guidelines on the state of the art in diagnosis and treatment of myelodysplastic syndromes and the key points of these recommendations are presented in two issues of the Belgian Journal of Hematology.[1] In this first paper we present the requirements for a correct diagnosis and classification of patients with myelodysplasia.
(Belg J Hematol 2015;6(1):10-5)

Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of haematological disorders. Accurate diagnosis of MDS is challenging, even for experienced hematopathologists. Many other conditions can mimic dysplasia and accurate diagnosis relies on results from cytomorphological review of blood and bone marrow, bone marrow pathology and cytogenetics. Since MDS is often suspected in very elderly patients in whom clinicians are often reluctant to do a full diagnostic work up, these patients are at risk of under- or misdiagnosis. These guidelines provide the minimal requirements for an accurate diagnosis of this condition.

Patient evaluation

A full medical history of the patient should be taken including current and previous drug intake, alcohol intake, professional or accidental exposure to toxic agents as well as the transfusion history. The majority of MDS patients are over the age of 70. Consequently, a high prevalence of co-morbid diseases has been reported in MDS patients and assessment of these co-morbidities is essential for defining individual follow-up schedules as well as optimising supportive care.[2] The presence of co-morbidities has a significant impact on non-leukemic death as well as overall survival, especially in very low and low-risk WHO classification-based Prognostic Scoring System (WPSS) patients.[3] In high-risk MDS patients, the clinical relevance of mild or moderate co-morbidity is overcome by the severity of MDS. In these patients, however, co-morbidity influences the outcome by limiting both eligibility and tolerance to treatment.[2]

A time-dependent MDS-specific co-morbidity index (MDS-CI) was developed for predicting the effect of co-morbidity on outcome. The MDS-CI was created by taking into account a selection of cohorts relevant to MDS from well-known indices (the Charlson Co-morbidity Index (CCI) and the Hematopoietic Cell Transplantation co-morbidity index (HCT-IC) by Sorror).[4] Landmark survival analyses at fixed time points from diagnosis showed that the MDS-CI can improve the

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: BHS, guidelines, MDS, myelodysplastic syndromes, review.

Table 1. WHO 2008 Classification of myelodysplastic syndromes.

Disease	Blood findings	Bone marrow findings
Refractory cytopaenias with unilineage dysplasia (RCUD) Refractory anaemia (RA) Refractory neutropenia (RN) Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia No or rare blasts (<1%)	Unilineage dysplasia; ≥10% of the cells of the affected lineage are dysplastic <5% blasts <15% of the erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only ≥15% of erythroid precursors are ring sideroblasts
Refractory cytopaenia with multilineage dysplasia (RCMD)	Cytopaenia(s) No or rare blasts (<1%) No Auer rods <1x10^9/l monocytes	Dysplasia in ≥10% of cells in two or more myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts No Auer rods ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopaenia(s) <5% blasts No Auer rods <1x10^9/l monocytes	Unilineage or multilineage dysplasia 5-9% blasts No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopaenia(s) 5-19% blasts Auer rods ± <1x10^9/l monocytes	Unilineage or multilineage dysplasia 10-19% blasts Auer rods±
Myelodysplastic syndrome – unclassified (MDS-U)	Cytopaenias ≤1% blasts	Unequivocal dysplasia in less than 10% of cells in one or more myeloid cell lines <5% blasts
MDS associated with isolated del(5q)	Anaemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

prediction of life expectancy of MDS patients stratified according to the WPSS.[2] It is therefore recommended to use the MDS-CI when planning treatment strategies in MDS patients. In addition, a Comprehensive Geriatric assessment (CGA) is recommended in patients aged 70 years or older.

Diagnostic investigations

Peripheral blood

A general blood analysis should be performed to rule out other possible causes of cytopaenia. In lower-risk patients with symptomatic anaemia, endogenous serum erythropoietin (EPO) levels should be obtained. Iron status (i.e. serum ferritin and transferrin saturation) is mandatory at diagnosis in patients who are transfusion dependent or who are starting transfusion. Microscopic evaluation of a peripheral blood smear is mandatory in all cases with unexplained cytopaenias and enumeration of peripheral blasts is necessary for classification purposes.

Bone marrow cytomorphology

The diagnosis of MDS relies on cytological examination of a bone marrow aspirate. This examination should include the determination of the degree of abnormal hematopoietic cell maturation or 'dysplasia' (at least 10% of cells of a certain lineage need to be dysplastic). Also the number of dysplastic lineages hold prognostic importance (uni- versus multilineage), the presence/absence of Auer rods and the percentage of myeloblasts.

Table 2. International Prognostic Scoring System (IPSS).

Score Prognostic variable	0	0.5	1	1.5	2
BM blasts (%)	<5	5 - 10		11 - 20	21 - 30
Karyotype*	Good	Intermediate	Poor		
Cytopaenias**	0 / 1	>2			

Risk group	Score	Median survival (years)	Time to AML transformation (years)
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.1
High	≥2.5	0.4	0.2

BM: bone marrow.
**Karyotype: Good: normal, -Y, del(5q), del(20q); Intermediate: +8, other abnormalities;*
Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies.
***Cytopaenias: Haemoglobin <10 g/dL, ANC <1.8 x 10^9/L, platelets <100 x 10^9/L.*

An iron staining is mandatory to look for the presence of ring sideroblasts and to estimate iron content. To determine the percentage of myeloblasts in cases of AML with > 50% erythroblasts, it is mandatory to calculate the number of blasts on the total of nucleated non-erythroid cells. The WHO 2008 does not make a statement on this in cases of MDS, but the BHS working group advices to do so.[5]

Trephine biopsy of bone marrow

When MDS is suspected it is also mandatory to perform a bone marrow biopsy. This biopsy gives important additional information on the global cellularity (ratio of hematopoietic cells versus adipocytes), the presence/absence of fibrosis, and the presence of abnormal localisation of immature progenitors (ALIP) and is needed to exclude other causes of cytopaenias (e.g. hairy cell leukaemia). It is also useful to detect dysplasia in the megakaryocytic lineages since these cells can be difficult to detect in a smear. The marrow of patients with MDS is often hypercellular, but hypocellularity can be detected in a minority of patients and these patients tend to respond better to immunosuppressive therapies.[6] The presence of marrow fibrosis also holds prognostic importance.[7]

Flow cytometry of bone marrow

In addition to standard bone marrow aspiration and biopsy, flow cytometry is a promising tool for the diagnosis of MDS. The European LeukemiaNet proposed a guideline to assess dysplasia by flow cytometry.[8] Since experience is currently lacking in many diagnostic centres, the expert panel does not recommend flow cytometry at this time for diagnostic or prognostic purposes. It is however very useful to differentiate between other bone marrow failure syndromes such as Large Granular Lymphocyte (LGL) leukaemia or hairy cell leukaemia. The percentage of myeloblasts is often underestimated with flow cytometry. In some patients with MDS, a paroxysmal nocturnal hemoglobinuria (PNH) clone can be detected with flow cytometry (peripheral blood sample is used) These patients tend to benefit from immunosuppressive treatments.[9]

Cytogenetic analysis

Cytogenetic analysis of bone marrow cells is a key requisite for accurate diagnosis and prognostication of patients with MDS; it should therefore be performed in every case of persisting cytopaenia without an apparent cause, even in the very old population. In addition to standard metaphase banding, fluorescence in situ hybrid-

Table 3. Revised International Prognostic Scoring System (IPSS-R).

Score Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics*	Very Good		Good		Intermediate	Poor	Very Poor
BM blasts (%)	≤2		>2-<5		5-10	>10	
Hb (g/dL)	≥10		>8-<10	<8			
Platelets (x10⁹/L)	≥100	≥50–<100	<50				
ANC (x10⁹/L)	≥0.8	<0.8					

Risk category	Median overall survival (years)	Median time to AML evolution (years)
Very low (≤1.5)	8.8	Not reached
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

ANC: absolute neutrophil count; BM: bone marrow; Hb: haemoglobin.
**Cytogenetics: 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 independent clones]; Poor [-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), 3 abnormalities]; Very Poor [>3 abnormalities].*

isation (FISH) is used to detect clonal abnormalities. After initial diagnosis, it is recommended to repeat a bone marrow aspirate when the clinical condition of the patient alters (e.g. start of or increasing transfusion need, appearance of peripheral blasts) and to evaluate response to treatments. As clonal evolution alters the prognosis of patients, it is also recommended to repeat the cytogenetic examination at that time.

Molecular analysis

Molecular analysis adds to the diagnosis, particularly to exclude other myeloid malignancies (e.g. chronic myeloid leukaemia) that can present with dysplasia. The JAK2V617F mutation is found in a subset of patients with MDS, especially in patients with RARS and thrombocytosis (RARS-T). An increasing number of mutations in genes responsible for DNA methylation, ribosomal proteins, spliceosome, etc. are found that show diagnostic, prognostic and therapeutic importance.[10] To date, the panel agrees that these should not be part of standard work up evaluation of a patient with MDS. It can be recommended to determine HLA-DR15 status in patients who are considered for immunosuppressive treatments since HLA-DR15$^+$ patients respond better to this treatment.[11]

Classification

FAB and WHO 2008

MDS staging and classification schemes have evolved significantly over the past few decades. The French-American-British (FAB) classification was the first and five subtypes of MDS were recognised based on the number of blasts in blood and bone marrow, the presence/absence of ring sideroblasts, and the presence of monocytosis.[12] The reimbursement of 5-azacitidine (Vidaza®) in Belgium still relies in part on the FAB classification. Since then, the classification of MDS has largely been refined. These refinements account for the

Key messages for clinical practice

1. **Accurate diagnosis of myelodysplastic syndromes should include a bone marrow biopsy and cytogenetics in every patient.**
2. **Patients should be classified according the WHO 2008 classification. The revised IPSS is the most accurate prognostic score.**
3. **In elderly patients, co-morbidities and performance status should be assessed at diagnosis and at the time of planning new treatment.**

number of affected myeloid lineages (uni- versus multi-lineage dysplasia), the number of myeloblasts (> 20% is defined as myeloid leukaemia) and the presence of the specific cytogenetic abnormality del(5q). Due to different clinical presentation and prognosis, CMML is currently classified as a MDS/MPN. *Table 1* summarises the WHO 2008 classification of MDS.

Prognostic Scores: IPSS and IPSS-R

The prognosis of patients with MDS is highly variable. Apart from the intrinsic prognostic value of the morphological classifications (FAB and WHO), a number of prognostic scores are currently in use in MDS. The most commonly used is the International Prognostic Scoring System (IPSS) which dates from 1997. The IPSS was defined on a large group of newly diagnosed untreated patients with MDS and calculates prognosis based on the number of myeloblasts, the presence of cytopaenias and the presence of cytogenetic abnormalities. It is still used to date and is also used for reimbursement purposes of several new drugs (e.g. 5-azacitidine and deferasirox).[13] The system has several limitations: it is limited to newly diagnosed patients, relatively little weight is based on the cytogenetics and is not accurate for very low-risk patients (e.g. unilineage dysplasia) (*Table 2*).

Over the last years, it has been demonstrated that transfusion-dependency is of prognostic importance. The WPSS was based on the WHO 2001 classification and the need for transfusion of packed cells.[14] The prognostic importance of different cytogenetic abnormalities has also been largely refined. An international dataset merge has led to the proposal of five different cytogenetic subgroups (*Table 3*).[15] This classification has been adopted by the revised IPSS (IPSS-R).[16] Apart from refining the cytogenetic subgroups, the depth of cytopaenias has been categorised for each cell line; to recognise the very low-risk MDS patients, the bone marrow blast percentage (0–2%, >2–<5%) has been split (*Table 3*). This scoring system will be the new standard for the following years.

Conclusion

The diagnosis of MDS is challenging. A correct diagnosis should be made by interpreting the results from cytomorphology, the bone marrow biopsy as well as the cytogenetics. Since adequate treatment and accurate prognosis relies on the diagnosis, all these diagnostic tools should be performed on every patient, irrespective of age.

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