HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Guidelines

Part 2: Myelodysplastic syndromes – classification systems

Irene Lorand-Metze[a,*], *Lígia Niero-Melo*[b], *Renata Buzzini*[c], *Wanderley Marques Bernardo*[c]

[a] *Instituto Nacional de Ciência e Tecnologia do Sangue da Universidade Estadual de Campinas (Hemocentro Unicamp), Campinas, SP, Brazil*

[b] *Faculdade de Medicina de Botucatu da Universidade Estadual Paulista (FMB UNESP), Botucatu, SP, Brazil*

[c] *Associação Médica Brasileira (AMB), São Paulo, Brazil*

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Objective

To discuss the classification systems that exist for myelodysplastic syndromes and which ones are recommended.

PICO system

Using the PICO system, the P corresponds to patients with myelodysplastic syndromes, I to the indicator of the classification system and the O to the outcome (prognosis, classification).

Thus, 14 studies were found and selected to answer the clinical question (Appendix I).

What classification and risk stratification systems exist for myelodysplastic syndromes and which should be used?

Introduction

In a review of classifications of myelodysplastic syndromes (MDS), Steensma wrote "Classifications and taxonomies are, by nature, artificial: simple mental constructs imposed upon an ambiguous and complex physical reality, and, therefore intrinsically imperfect".[1] This statement is important to remember when dealing with MDS that is a group of very heterogeneous pre-leukemic conditions associated with clonal hemopoiesis. However, in patients' daily care, as well as in clinical studies, some systematization is necessary as a working principle.

The first attempt of a classification of these disorders was made by the French-American-British (FAB) Cooperative Group in 1982.[2] It described five categories based on data of peripheral blood (PB) and bone marrow (BM)

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* Corresponding author. Instituto Nacional de Ciência e Tecnologia do Sangue da Universidade Estadual de Campinas (Hemocentro Unicamp), R. Carlos Chagas, 480, Cidade Universitária, Campinas, SP, Brazil, CEP: 13083-878.
E-mail address: ilmetze@unicamp.br (I. Lorand-Metze).

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cytology. It is still used in some publications.[3] This classification also had some prognostic value, but it was merely descriptive and was not able to classify several cases. Somehow it permitted the study of MDS characteristics better, and with new knowledge acquired about cytogenetics, phenotyping and molecular features, the World Health Organization (WHO) improved the classification of MDS in 2001; this classification was modified in 2008[4] and again in 2016. This classification was always improved to include new relevant information published about the pathophysiology and clinical behavior of the MDS types.

The WHO classification is not only based on features obtained from PB values and BM morphology, but it also includes cytogenetic findings, which clearly began to define some pathological entities, and that nowadays have specific treatment (5q- syndrome). Even some aspects discovered by molecular analysis were included in the 2016 update,[5] thus giving support to new therapies.

Switching from FAB to WHO, chronic myelomonocytic leukemia was removed from the MDS group and included in that of myelodysplastic/myeloproliferative disorders, as it has more proliferative features. Furthermore, the threshold of 20% of BM blasts separating MDS and acute leukemia was chosen and so Refractory Anemia with Excess Blasts in Transformation (RAEB-t) was considered acute myeloid leukemia (AML). However, it is recognized that this threshold is artificial concerning therapeutic decisions. The features of BM histology were not considered to define an entity, hence, the WHO classification was able to stratify cases with BM blasts <5% better. Accordingly, in a Brazilian study of 150 patients,[6] one-third of the patients, mainly cases with BM blasts <5%, changed category. The 2016 update split all categories into 'with and without ring sideroblasts'. In addition, the old AML FAB M6 was included in MDS as RAEB if the percentage of blasts of non-erythroid cells in BM was <20% and as AML if BM blast percentage of all nucleated cells was ≥20%.

The main prognostic factors in myelodysplastic syndromes (MDS) are associated with the degree of BM failure (peripheral cytopenias), the percentage of blasts in BM aspirate, as well as cytogenetic alterations. Anemia, the most common cytopenia, can cause transfusion dependence and consequently iron overload, with its vicious circle of morbidity and mortality.

The percentage of blasts in BM aspirate, which is related (but not equal) to the number of $CD34^+$ cells counted by cytometry or evaluated in the BM by immunohistochemistry, is a measure of the abnormal clone lesion and its proliferation. These parameters may indicate clonal progression and/or leukemic transformation. The number and type of phenotypic changes, as well as the type of cytogenetic changes found are also evidence of this fact.

Extraction of results

Which prognostic classification system should be used?

Since the French-American-British (FAB) classification system was described, prognosis was defined generally based on the percentage of blasts in the BM. The WHO classification, which is based not only on the number of BM blasts, but also on the degree of atypias of hematopoietic lineages, allowed a better stratification of the low-risk types. In 1997, the International Prognostic Score System (IPSS) was described after analyzing 816 cases; it is based on the number of cytopenias, percentage of BM blasts and the type of cytogenetic alteration (Table 1)[7] (B). This index has been widely used to indicate allogeneic BM transplantation, to choose the treatment of patients and for their inclusion in clinical studies.

With the refinement of the knowledge about cytogenetic changes and their impact on prognosis, the International Working Group for the Prognosis of MDS (IWG-PM) conducted a multicenter study of 7012 patients (including Brazilian patients). This study analyzed the effect of complete blood counts (CBCs), the percentage of blasts in BM aspirate and the cytogenetic risk groups on the prognosis and subsequently revised the IPSS (IPSS-R)[8,9] (B). The revised index categorizes the data of CBCs and the percentage of marrow blasts in more detail (Table 2).

Furthermore, based on 1314 cases, Italian and German authors described a prognostic score that, in addition to the parameters of the CBC, includes the type of MDS based on the WHO classification, as well as the presence or not of transfusion dependence (WHO Prognostic Scoring System - WPSS). More recently, they replaced 'transfusion dependence' with the hemoglobin value[10] (B). This index can be applied not only at diagnosis, but also during the evolution of the disease (Table 3).

There are also a number of other prognostic scores (Lille, German, MD Anderson), that value different clinical and bio-

Table 1 – International prognostic score system (IPSS) classification of myelodysplastic syndromes.

Prognostic variable	IPSS score				
	0	0.5	1.0	1.5	2.0
% BM blasts	<5	5–10	–	11–20	21–30
Cytogenetics	Favorable	Intermediate	Unfavorable	–	–
Cytopenias	0–1	2–3	8 < 10	<8	–

Risk category	IPSS score	Overall survival (years)
Low	0.0	5.7
Intermediate I	0.5–1.0	3.5
Intermediate II	1.5–2.0	1.2
High	≥2.5	0.4

Table 2 – Revised International prognostic score system (IPSS-R) classification of myelodysplastic syndromes.

Prognostic variable	IPSS-R score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
% BM blasts	≤2	–	>2–<5	–	5–10	>10	–
Cytogenetics	Very good	–	Good	–	Intermediate	Bad	Very bad
Hemoglobin - g/dL	≥10	–	8–<10	<8	–	–	–
Platelets – × 10^9/L	≥100	50–<100	<50	–	–	–	–
Neutrophils – × 10^9/L	≥0.8	<0.8	–	–	–	–	–

Risk category	IPSS-R score	Overall survival (years)
Very low	≤1.5	8.8
Low	>1.5–3	5.3
Intermediate	>3– 4.5	3.0
High	>4.5–6	1.6
Very high	>6	0.8

Table 3 – Revised WHO Prognostic Scoring System (WPSS) including the degree of anemia.

Variable	Variable score			
	0	1	2	3
WHO category	RARS, RCUD, MDS associated with del(5q) or not	RCMD	RAEB-I	RAEB-II
Karyotype*	Good	Intermediate	Bad	–
Severe anemia (Hb <9 g/dL in men and Hb <8 g/dL in women)	Absent	Present	–	–

WPSS risk	Sum of variable scores
Very low	0
Low	1
Intermediate	2
High	3–4
Very high	5–6

RARS: Refractory anemia with ring sideroblasts; RCUD: Refractory cytopenias with unilineage dysplasia; MDS: Myelodysplastic syndromes; RCMD: Refractory cytopenia with multi-lineage dysplasia; RAEB-I: Refractory anemia with excess blasts-1; RAEB-II: Refractory anemia with excess blasts-2.

* Good (normal, -Y, del(5q); Bad (complex, abnormalities of chromosome 7); Intermediate: other chromosomal abnormalities.

chemical parameters in addition to those used in the IPSS (B),[11,12] but these are less used by groups studying MDS. On analyzing 1915 patients, the MD Anderson Hospital group described a prognostic index that, in addition to the variables used in the main scores, adds the patient's age and patients' performance status (MD Anderson Score - MDAS and Low-risk Prognostic Scoring System - LR-PSS)[13,14] (B).

Moreover, because it is a geriatric population, it is important to evaluate the comorbidities (cardiac, hepatic, renal, pulmonary and presence of solid tumors) presented by patients. Thus, the Italian Group described a Comorbidity Index (MDS-CI) after analyzing 1344 cases[15] (B). In addition to the IPSS category of each patient, other risk factors are taken into account. These include the degree of anemia (WPSS) and iron overload, lactic dehydrogenase and beta-2-microglobulin levels, comorbidities (mainly cardiac), cytogenetic risk (five categories), phenotypic abnormalities of $CD34^+$ cells and data obtained by BM biopsy such as fibrosis, clusters of $CD34^+$ cells (formerly called atypical localization of immature precursors - ALIPs), and degree of megakaryocytic dysplasia, as well as specific molecular alterations[16] (B).

Prognostic indexes are useful tools to assess the risk of leukemic transformation, estimate life expectancy and optimize therapeutic decisions. For high-risk patients, the goal of therapy is to extend overall survival (OS) and delay leukemic transformation, using cytotoxic regimens similar to those used for AML. However, these regimens are considered very toxic for low-risk patients where the goal of therapy is to improve cytopenias and quality of life.

Since the description of the first prognostic index (IPSS) in 1997, more than 15 proposals have been published. The most widely used indexes (IPSS, IPSS-R, WPSS and MD Anderson) were described after the analysis of large multicenter patient databases, and validated by researchers who did not participate in the initial study. However, they all have their limitations, especially for analyzing low-risk patients. MDS are a group of very heterogeneous entities from both genetic and molecular points of view, where we still do not know all the aspects involved[16] (B). However, so far, the analysis of all features is not feasible in the daily clinical practice, but with the advancement of therapy, there is an increasing need to separate cases that are responsive to certain treatments.

The prognostic value of the various scores in the different populations studied has been poorly reproducible either due to the insufficient number of cases enrolled or because of the short observation time. Low-risk cases in particular, which are

the majority in all cohorts, require a very long observation time (more than 10 years) to have a significant number of events. In addition, the methodology used should be taken into account, since these patients are elderly, have comorbidities and thus only events caused by MDS should be considered and not those related to comorbidities.

Comparison of the prognostic value of different scores

The IPSS-R prognostic value was evaluated by multivariate analysis in a retrospective study of 173 patients and compared to the IPSS, MDAS, WPSS and WPSS-R. The mean follow-up was 17 months. The IPSS-R, compared to the IPSS, MDAS, WPSS and WPSS-R, had better prognostic power for all risk groups except for high-risk and very-high-risk patients (B);[17] but as stated above, the observation time was too short for low-risk patients.

A retrospective study of 173 adult MDS patients who had not received disease-altering treatment was performed to externally validate the IPSS-R and compare it with IPSS. In the univariate analysis, the IPSS-R was a significant predictor of survival and time to transformation to AML (p-value <0.001). The IPSS-R had better prognostic power for survival and transformation time to AML when compared to the IPSS (Somers' D values: 0.41 vs. 0.39 and 0.55 vs. 0.53, respectively)[17] (B).

The Dutch Group, on comparing the value of the MDS-CI with the IPSS-R, showed by multivariate analysis that the MDS-CI significantly improved the IPSS-R risk stratification (p-value <0.000). By analyzing the MDS-CI subgroups separately, IPSS-R had a significant prognostic value for OS in low and intermediate MDS-CI risk patients (p-value <0.000), but not in the high-risk group (p-value = 0.057)[11] (B).

The IPSS, IPSS-R and the MD Anderson score were compared with the low-risk score (LR-PSS) to assess low-risk patients who may have a worse prognosis. The mean observation time was 62 months. The Cox model and the Akaike information criterion (AIC) were used to compare models to validate the results[12] (B). While both LR-PSS and IPSS-R distinguish groups with varied survival outcomes among patients with IPSS LR-MDS, both tools fail to identify a significant subset with poor OS.

In an analysis of 775 patients retrospectively assessed after a mean follow-up of 55 months, the transformation rate to AML was significantly different between the MDAS subgroups (p-value <0.005). After multivariate analysis, the IPSS and MDAS were independent prognostic factors of OS[18] (B).

On comparing the IPSS and WPSS of 149 patients with a mean follow-up of 39.2 months, the WPSS presented excellent patient risk stratification according to OS and time to leukemic transformation and contributed to the stratification of patients into five subgroups of risk for death and progression to leukemia (p-value <0.0001). For the IPSS, the cytogenetic risk and the percentage of blasts in the BM were correlated to the OS and leukemia-free survival, which was not true for the number of cytopenias. For the WPSS however, cytogenetics and transfusion dependence were statistically significant in respect to OS and time of progression to leukemia[19] (B).

Furthermore, the Dutch Group studied a population of 222 patients with a mean age of 66 years followed up for an average of 22 months. The differences in the mean OS were significant for all five prognostic score systems. Differences in the mean leukemia-free survival were significant for WPSS, WPSS-R, MDAS and IPSS-R, in contrast to IPSS (p-value = 0.016, p-value = 0.003, p-value <0.000, p-value = 0.001 and p-value = 0.086, respectively)[11] (B).

The influence of the IPSS, IPSS-R, WPSS and immunophenotypic changes on the OS of patients with MDS who were always censored when undergoing chemotherapy or BM transplantation was studied in Brazilian patients in a single-institution study. One hundred and one patients were enrolled with a median age of 64 years and a median follow-up time of 28 months. Most patients were at low or intermediate risk according to the prognostic scores. In a multivariate analysis comparing IPSS, IPSS-R and WPSS, only IPSS-R remained in the model. Each prognostic score was also compared with immunophenotyping data. In a multivariate model with IPSS, total phenotypic changes and the percentage of myeloblasts calculated by cytometry, only the two last parameters remained in the model. With WPSS and immunophenotyping, only WPSS and the percentage of myeloblasts calculated by cytometry remained in the model. Finally, comparing the IPSS-R with immunophenotyping, only IPSS-R and the percentage of myeloblasts calculated by cytometry were left in the model. Thus, the percentage of $CD34^+/CD13^+$ cells (myeloblasts by cytometry) was an independent risk factor in the three prognostic scores assessed[20] (B).

Recommendations

The IPSS-R has greater prognostic power for all risk groups when compared to IPSS, MDAS, WPSS and WPSS-R as it identifies a large group of patients with better OS. However, among low-risk patients, no index was able to predict poorer outcomes in some patients. MDS-CI significantly increased the prognostic value for OS in patients stratified by the IPSS-R. The IPSS-R increased the predictive power of leukemia-free survival and OS of patients when compared to IPSS and WPSS. The WPSS distinguishes the very low-risk patients who present excellent survival with rare evolution to leukemia, while the IPSS does not have the same discriminatory power. Thus, in the clinical practice, the IPSS-R is currently the best index.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix I

1. Clinical question
   What classification systems exist for myelodysplastic syndromes and which should be used?
2. Structured question (PICO)

Patient	Patients with MDS
Intervention	IPSS IPSS-R WPSS WPSS-R MD-IPSS (MD Anderson Cancer Center MDS score) LR-IPSS (MD Anderson Cancer Center score for low-risk MDS)
Comparison	None
Outcome	Classification of prognosis

3. Initial eligibility criteria for studies[21,22]
   - Components of PICO
   - No time limit
   - No limit of languages
   - Full text availability
4. Search strategies
   #1: (Myelodysplastic Syndrome OR Myelodysplastic Syndromes OR Dysmyelopoietic Syndromes OR Dysmyelopoietic Syndrome OR Hematopoietic Myelodysplasia OR Hematopoietic Myelodysplasias) = 23,074 studies
5. Selection of articles
   Initially selected by the title, sequentially by the abstract, and finally by the full text, the latter being subjected to critical evaluation and extraction of outcomes related to the outcomes.
6. Critical evaluation and strength of evidence
   The strength of the evidence of the studies was defined taking into account the study design and the corresponding risks of bias, the results of the analysis (magnitude and precision), relevance and applicability (Oxford/GRADE).

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