Review article

The evolving clinical scenario of myelodysplastic syndrome: The need for a complete and up to date upfront diagnostic assessment

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A B S T R A C T
Until the beginning of the current millennium, few concrete therapeutic possibilities were available for myelodysplastic syndrome (MDS) patients. This situation has dramatically changed in the last decade when new knowledge, new drugs and new opportunities have become available for physicians and their MDS patients. A correct diagnostic and prognostic assessment of all MDS patients wherever they are first seen in a hematology or internal medicine department is mandatory to identify the best therapeutic option and the most appropriate resources allocation. This article will review modern diagnostic criteria and classification together with correlated new therapeutic opportunities.

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1. Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by impaired peripheral blood cell production (cytopenias) and most commonly a hyper cellular dysplastic—appearing bone marrow [1–3].

The first report describing one hundred patients with refractory anemia was published in 1938 [4]. In 1953 the term pre-leukemia was coined [5]. The extreme variability of disease’s manifestations led to the development of various classification attempts.

In 1976 the French–American–British (FAB) Cooperative Group used the term myelodysplastic syndrome to classify this kind of anemia [6]. At present the World Health Organization (WHO) is the main reference classification for MDS [7]. It was reviewed in 2008 [1] and takes into account the cytopenias and a number of bone marrow blasts as main discriminant between myelodysplastic subtypes.

2. Epidemiology

The exact prevalence of MDS in the world population is unknown. Myelodysplastic patients are often classified under other disease categories in internal medicine or the anemia is not investigated for a possible myelodysplastic diagnosis. In the United States prevalence is estimated to be about 10,000 cases annually [8] with an incidence of 3–12 new cases every 100,000 person/year [9].

All the epidemiologic studies have underlined that incidence increases with age [8,10,11]. The median age to develop this disease is 65 years, with a male prevalence [8]. Onset of the disease before 50 years is infrequent [12,13] and often associated to previous chemotherapy (treatment – induced MDS) [14].

3. Diagnosis, why is it so difficult?

Diagnosis of MDS is complex and often misunderstood for its extreme variability in presentation and associated symptoms. Many patients are asymptomatic, others are diagnosed only after routine laboratory screening [15]. The following paragraphs detail the most frequent symptoms of MDS: however, the presence and effects of co-morbidities pose a particular challenge in elderly patients. Unfortunately, a specific, validated co-morbidity score is not, so far, available for MDS patients.

3.1. Signs and symptoms

Anemia and correlated signs and symptoms (fatigue, weakness, exercise intolerance, angina, dizziness, and cognitive impairment) are the most relevant, disease-specific manifestation resulting in an accepted MDS diagnosis [16] (Table 1). Anemia is often associated with other cytopenias (neutropenia or thrombocytopenia). Many epidemiologic studies have examined the incidence of MDS syndrome in elderly patients [17–19]. Joosten et al. showed that the 5.5% of elderly patients admitted for unknown anemia were subsequently diagnosed with MDS or acute leukemia [20]. Anemia could be associated with neutropenia and thrombocytopenia in up to 50% of MDS patients. Only approximately 5% of patients present with isolated neutropenia or thrombocytopenia without anemia [21].
Thrombocytopenia was present in the 37% of 816 MDS patients enrolled in the original Greenberg international prognostic score system (IPSS) study [22]. An extensive literature review indicated that the prevalence of thrombocytopenia (platelets < 100 × 10^9/l) in MDS ranged from 40% to 65%; however only 7% of patients showed isolated thrombocytopenia at diagnosis. Thrombocytopenia’s prevalence increases in highest IPSS categories [23].

Low neutrophil counts and a granulocyte dysfunction (in chemotaxis and microbial killing) can lead to recurrent infection [24,25]. Skin, lungs and kidney are the most common sites of infection [24]. Infections are the principal cause of death in MDS patients [24,26].

Bruising and bleeding manifestations are less common.

Co-existing autoimmune dysfunctions pose a particular challenge for MDS diagnosis: polyarthritis, polymyalgia rheumatica, Sjogren’s syndrome, Raynoud phenomenon, inflammatory bowel disease and glomerulonephritis have all been reported in association with MDS. They have been called paraneoplastic autoimmune complications [27,28]. Fourteen percent of 221 reviewed MDS patients experienced cutaneous vasculitis and mono articular arthritis as presenting symptoms [27]. Hepatomegaly, splenomegaly and lymphoid adenopathy are however uncommon [21].

### 3.2. Morphology

Peripheral blood film and bone marrow aspirate examinations are essential for MDS diagnosis, to establish the presence of abnormal peripheral blood cell production (cytopenias) and of dysplastic features in bone marrow [2,3]. For detailed illustration and descriptions see www.siematologia.it e-learning section.

#### 3.2.1. Erythropoiesis

Characteristic features on a peripheral blood film usually include: macrocytosis (less commonly normocytosis), anisocytosis (variation in size of erythrocytes), poikilocytosis (abnormally shaped erythrocytes), basophilic stippling (aggregation of ribosomal RNA in erythrocytes cytoplasm), Howell–Jolly bodies (inclusion of nuclear chromatin remnants), megaloblastoid nucleated red cells, pseudo-erythroblasts (mature erythrocytes retaining their reticulofilamentosa substantia).

Examination of bone marrow aspirates shows erythroid hyperplasia with dyserythropoietic features such as nuclear-cytoplasmic asynchronism in maturation, megaloblastoid features, intranuclear bridging (intranuclear microtubule organization), karyorrhexis and karyopiknosis (differential stage of cellular necrosis in which the fragments of the nucleus and its chromatin are distributed irregularly throughout the cytoplasm) [29,30]. Increase of ring sideroblasts containing iron granules are underlined by the Perls stain. They are caused by iron storage in bone marrow and are characteristic of a specific subtype of MDS (refractory anemia with ringed sideroblasts – RARS) [31]. Red cell hypoplasia may rarely occur [32].

#### 3.2.2. Granulopoiesis

Neutrophil shows dysplastic features such as hypo-granularity and acquired Pelger-huet anomaly (hypo-segmentated or bi-lobated polymorphonuclear leucocytes) and ring-shaped nuclei [31,33–35].

#### 3.2.3. Megakaryopoiesis

Giant platelets or megakaryocyte fragments may be present in peripheral blood film. Bone marrow’s megakaryocytes maturation show dysplastic features like small size (micromegakaryocytes) multiple disperse nuclei, hypo-lobated nuclei and hypo-granularity. They appear normal or increase in number and in some instances cluster forming [33,36,30]. Platelet count is often reduced but in a minority of patients it may be increased. Thrombocytopenia in association with small megakaryocytes with hypo-lobated nucleus is the main feature of the 5q- syndrome [37].

### 3.3. Histology

Bone marrow biopsy has acquired a more significant role in MDS diagnosis. Abnormal localization of immature precursors (ALIP) is common, particularly in the advanced MDS subtype. Granulocytes precursors are displaced from their paratrabecular location to more central marrow suggesting a high risk of progression to acute leukemia [38].

Increase in reticular fibres (present in up to 50% MDS patient’s bone marrow), results in different grades of fibrosis, which can be appreciated by a silver impregnation stain [39]. MDS patients with hyper fibrotic bone marrow often develop pan-cytopenia and tri-lineage dysplasia correlating with poor prognosis outcome [40].

### 3.4. Cytogenetic

Cytogenetic studies in addition to provide diagnostic confirmation, are important for prognosis and are essential for outcome prediction and treatment planning [22,41,42].

Bernasconi et al. showed in 2005 the relative incidence of karyotypic abnormalities in a large group (n = 331) of de novo primary MDS patients: normal: 40%, − Y: 7%, Del5(q): 8%, Del20(q): 2%, chromosome 7 abnormalities: 8%, complex karyotyping: 20%. Chromosome alterations are clearly correlated with outcome. More than two thousand MDS patients were studied by Haase et al. [43]. Median survival was 53.4 months for patients with normal karyotypes and 8.7 months for those with complex abnormalities.

The 5q- gene mutation characterizes a particular subgroup of MDS patients: when this cytogenetic abnormality is isolated and associated with particular characteristics and bone marrow features (<5% blast cells in bone marrow, thrombocytoma with small hypo-lobated megakaryocytes in bone marrow, macrocytic anemia with transfusion dependency) it identifies the presence of the 5q- syndrome which represent a subtype of MDS. This is the first MDS subtype which is identified by a specific single cytogenetic mutation and specific phenotypic characteristics. The incidence of the 5q- syndrome is approximately 10%, and it is more frequent in elderly females (age > 60 years). The 5q- syndrome is particularly responsive to the new developed immunomodulatory agent lenalidomide [44].

### 3.5. Other diagnostic/prognostic studies

Immunophenotyping could be helpful in selected case to quantify the percentage of myeloid precursor using antibodies to CD13, CD14, and CD33 [45], to assess the increase of megakaryocytic forms [46] and quantify the apoptotic cells. The increase of apoptotic cells in bone marrow has been reported to be a good prognostic feature [47,48]. Antibodies to CD 34 and 117 could also be useful in determining the amount and the pattern of bone marrow blast cells infiltration [49]. However, at the present time there isn’t enough evidence to support routine immunophenotyping at diagnosis.

The JAK2 V617F gene is usually undetectable in MDS patients. However, recently, a new subtype of MDS called JAK2 positive myelodysplastic–myeloproliferative syndrome has been included in the WHO classification [1]. This syndrome is characterized by hyper
cellular marrow and signs more typical of myeloproliferative syndromes, such as thrombocytopenia and splenomegaly [50].

In Table 2 the most frequent differential diagnosis options for MDS are reported.

### 4. Classification

The extreme variability of MDS is attested by the parallel development of various attempts of classification. The French–American–British (FAB) cooperative group in 1982 attempted the first MDS classification in 5 subtypes of disease [51]. This morphologic classification has been the main tool for physicians for more than 20 years. The recent advances in cytogenetic and molecular characterization led to the WHO classification which, nevertheless, remains substantially a morphologic classification. The 2002 [7] WHO classification excluded the Chronic Myelomonocytic Leukemia (CMML) from MDS and considered new MDS forms such as multi-lineage dysplasia, 5q- syndrome, and MDS/myeloproliferative syndrome. Furthermore, it decreased the threshold of maximal blast percentage required for the diagnosis of MDS from 30% to 20%. This is a very important shift, since traditionally only blasts percentage major or equal to 30% had been considered as diagnostic of acute leukemia. By grouping this heterogeneous disease in homogeneous subgroups, the WHO classification has profound clinical relevance, since it allows performing homogeneous treatment and testing new drugs and therapeutic strategies. Table 3 reports the WHO classification in 2008 version.

### 5. Prognostic score

The prognostic challenges for MDS patients were noticeably simplified with the pivotal clinical research paper performed by Dr Greenberg et al. in 1997. They developed a simplified prognostic classification system (International Prognostic Scoring System for MDS – IPSS) that permitted to classify all the MDS syndromes in four homogeneous, prognostic groups [22]. On the basis of three simple, reproducible and quantitative parameters (cytogenetic abnormalities, cytopenias and bone marrow blasts percentage) the IPSS classification estimates the median time to leukemia progression and survival (Table 4). Four groups were identified with a median time to leukemia progression and survival ranging from 0.2 to 9.4 and 0.4 to 5.7 years, respectively.

The IPSS classification was developed at a time when the category of refractory anemia with excess blasts in transformation (RAEB-t i.e. blasts percentage 20–30% of nucleated bone marrow cells) was still included as part of MDS. After 2002 the RAEB-t were excluded from the MDS and considered to be part of the acute leukemias. Thus, by adapting the IPSS to the new definition of MDS, the number of patients classifiable in the high-risk group has decreased significantly.

The IPSS is easy to calculate and quite reproducible, although it doesn’t consider age related co-morbidities and the greater impact of cytogenetic abnormalities. Attempts to review IPSS system are ongoing.

About 90% of all MDS patients with permanent anemia become dependent on blood transfusions to maintain their quality of life and to survive. Transfusion dependency has been shown to be associated with a poorer prognosis. Malcovati et al. included transfusion dependence and substituted the number of cytopenias with the WHO classification in a new prognostic index (WHO Prognostic Score System = WPSS) obtaining 5 prognostic groups [52,53] (Table 5).

While the IPSS is an upfront prognostic classification, a novel and potentially much useful feature of WPSS is its dynamic, time dependent nature, offering the possibility to re-classifying patients at any progression step during the course of their disease.

Although suffering of few limitations like the impact of anemia and transfusion dependence which are today evident, because of its proven reproducibility and track record, the IPSS score still remains the prognostic reference standard [54]. In clinical practice, outside specialized reference centers, the number of cytopenias represents a much more easy and reproducible feature than the complex morphologic WHO classification.

### 6. Therapy

The development of the prognostic scores, mainly the IPSS, has been a cornerstone of MDS research and clinical practice and must be applied to select the most appropriate treatment for each individual patient.

The prognostic scores have been developed when supportive care was the only available treatment. Now disease-modifying therapy has come to physicians’ attention and patients’ accessibility. Hopefully in the near future new prognostic prediction models and scores, which will consider therapy effect, will be available.

#### 6.1. Treatments for IPSS low and intermediate-1 risk patients

Several evidence-based therapy guidelines have been recently published and here we will reassume the most important recommendations.

It is usually recommended not to treat asymptomatic patients (no bleeding, no recurrent infections), patients with mild anemia (hemoglobin equal or greater than 10 g/dl, without symptoms), patients who have a percentage of blasts in bone marrow <5%, do not carry poor-risk cytogenetic, and do not show other severe cytopenias. This kind of patients does not need any treatment and can just be followed up over time.

Eighty percent of MDS patients present anemia or anemia in association with other cytopenias at diagnosis. Correction of anemia can have a great impact on quality of life [55]. Erythropoiesis stimulating agents should be considered if serum erythropoietin determination is <500 mU/ml and hemoglobin is <10 g/dl [56]. Several studies have been published on this issue and today with high doses recombinant human erythropoietin (60,000–80,000 units per week) in well selected patients a high rate of response (50–71%) can be achieved [56].

Despite a substantial fraction of MDS patients becoming transfusion dependent, there are not well-developed guidelines to manage chronic transfusion therapy [55]. A pre-transfusional hemoglobin threshold level of 9 g/dl is commonly used, although several centers use a lower threshold. For patients with cardiac disease a higher pre-transfusion hemoglobin level is usually adopted.

Transfusion dependent patients develop iron overload proportionally to the duration and intensity of transfusion dependency [57].
Indicators of iron overload such as high ferritin levels have been reported to be important adverse prognostic factors for MDS patients on supportive care. Among low risk MDS patients who died as a result of a non-leukemic cause cardiac failure was significantly more frequent in transfused patients. Cardiac iron accumulation has been demonstrated to develop in unchelated MDS patients, after receiving approximately 70–80 packed blood red cell units [58,59]. However the relationship between iron intake, cardiac iron deposition and cardiac function is still a matter of debate [60].

Although substantial disagreements persist on this topic [61,62], iron chelation therapy should be considered for all patients with low and intermediate-1 IPSS risk disease who receive regular red cell transfusions therapy [56,63,64]. Chelation therapy should be started after patient had received 20 packed red blood cell units (i.e. 4 g of iron) [56,63]. Deferasirox is recommended as first line therapy in MDS patient with clinically significant iron overload [56].

The National Comprehensive Cancer Network (NCCN) guidelines [65] in accord with the Italian Society of Hematology (SIH) recommend the use of the immunomodulatory agent lenalidomide as first line therapy within a clinical register or a clinical trial in patients IPSS low–intermediate-1 risk, transfusion dependent with 5q- cytogenetic abnormality. A complete hematologic and cytogenetic response is expected in about 70–80% of patients [66]. Lenalidomide could be a treatment option in the absence of the 5q- deletion as well, but with a much lower responsiveness [67]. The main adverse event of this drug is the dose-related myelo-suppressive effect, which correlates with better chance of clinical response to the drug [68]. Myelosuppression is reversible with the drug discontinuation followed by dose reduction [56]. Therefore a regular (i.e. weekly) monitoring of full blood count is required, especially during the first 2 months of treatment. Concerns on a possible, detrimental, selection effect of lenalidomide have not materialized in controlled prospective randomized trials [69].

### 6.2. Treatments for IPSS intermediate-2 and high-risk patients

Epigenetic modifications play a role and cooperate with genetic alterations in the pathogenesis of MDS. The potential reversibility of chromatin remodeling renders epigenetic events ideal targets for therapy. Hypo-methylating agents are the gold standard of therapy in patients without HLA match donor [56]. The hypo-methylating agents 5-Azacitidine and Decitabine can reverse epigenetic silencing and have been extensively used in the treatment of MDS patients.

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**Table 3**

MDS WHO 2008 classification [1].

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Peripheral blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Bi- or pan-cytopenia</td>
<td>Dysplasia in 10% of cells in two or more myeloid cell lines</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)</td>
<td>Bi- or pan-cytopenia</td>
<td>Dysplasia in 10% of cells in two or more myeloid cell lines</td>
</tr>
<tr>
<td>Refractory Anemia with Excess Blasts-1 (RAEB-1)</td>
<td>Cytopenias</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenias</td>
<td>Unilineage dysplasia</td>
</tr>
<tr>
<td>MDS-unclassified (MDS-U)</td>
<td>Cytopenias</td>
<td>Unilineage dysplasia in granulocytes or megakaryocytes</td>
</tr>
<tr>
<td>MDS with del(5q) “5q- syndrome”</td>
<td>Anemia</td>
<td>Normal to increased megakaryocytes with hypolobulated nuclei</td>
</tr>
</tbody>
</table>

Note: In this proposed WHO system, the FAB MDS subgroup refractory anemia with excess blasts in transformation (RAEB-T) has been taken out of the MDS classification and is now considered acute myeloid leukemia with multilineage dysplasia.

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**Table 4**

The International Prognostic Score System (IPSS) [22].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score 0</th>
<th>Score 0.5</th>
<th>Score 1</th>
<th>Score 1.5</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM BLAST (%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

The original score was developed when the category of refractory anemia with excess blasts in transformation (RAEB-T i.e. blasts percentage 20–30% of nucleated bone marrow cells — in grey in the table) was included inside the MDS. After 2002 the RAEB-T are excluded from the MDS and considered to be acute leukemias.

Good, normal, — Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

Original scores for risk groups are as follows: Low, 0; INT-1, 0.5–1.0; INT-2, 1.5–2.0; and High, ≥2.5.

Evolution to acute myeloid leukemia: low median 9.4 years; intermediate-1 median 3.3 years; intermediate-2 median 1.1 years; and high median 0.2 year.
The Food and Drug Administration approved Azacitidine in 2004 with the intent to treat every subtype of MDS [70]. The superiority of Azacitidine versus supportive care has been confirmed in a randomized phase III study conducted by the Cancer and Leukemia Group B. Response rate was 60% in Azacitidine group versus 5% in control arm [71]. Another prospective randomized trial comparing Azacitidine versus conventional therapy (best supportive care, low dose cytarabine or intensive chemotherapy as selected by investigators before randomization) demonstrated a significant better two years overall survival for Azacitidine (50.8% versus 26.2%) [72]. 

Azacitidine is administered via subcutaneous injection [73], with the main adverse event being myelotoxicity. The optimal duration of therapy with hypo-methylating agents is unknown, however continued Azacitidine treatment has been shown to further improve the quality of response [74]. 

Azacitidine is approved and reimbursed in approximately 30 countries worldwide but it is expensive. Recently the UK National Institute for Health and Clinical Excellence (NICE) issued a final ruling saying that Azacitidine should not be funded because it is not cost-effective [75]. 

Chemotherapy treatment AML-like remains an option only for selected cases (bone marrow blast percentage >10% and aged less than 65 years) refractory to hypo-methylating agents. 

6.3. Indication for allogeneic stem cells transplantation

Allogeneic hemopoietic stem cell transplantation (HSCT) remains the only proven curative treatment for MDS. Because MDS occurs in a population of older adults with significant co-morbidities, HSCT is indicated only in a minority of patients. Reduced-intensity and reduced-toxicity [76] conditioning regimens have been particularly important in expanding the use of HSCT to a larger MDS population. Co-morbidity, age, IPSS score, and donor selection are predictors of post transplant outcome [77, 78]. 

Allogeneic HSCT should be evaluated in all MDS patients <65 years with an HLA match donor (sibling or unrelated). The best candidates for allogeneic HSCT are usually considered patients with an IPSS risk intermediate-2 or high score or even a lower score but with a high rate transfusion dependency [56].

7. Conclusions

The aim of this review has been to underline the clinical importance of a correct diagnosis of MDS. During the last decade, we have experienced a rapid and significant change in both diagnosis and therapeutic approach for MDS. New low-toxicity and effective agents have become available and a larger portion of MDS patients has been treated. 

The WHO classification and IPSS score system are essential to guarantee the best therapeutic approach to any MDS patient. New drug combinations and several new agents are under investigation and hopefully in the near future, new and better therapeutic possibility will be available for consideration by physicians taking care of MDS patients.

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