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Review article

Myelodysplastic Syndromes (MDS); diagnosis, classification, treatment, and monitoring

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Abstract

Due to the neoplastic nature of myelodysplastic syndromes (MDS), they have been renamed as myelodysplastic neoplasms in the World Health Organization (WHO) 2022 classification. These syndromes are heterogeneous groups of myeloid disorders characterized by dysplasia of bone marrow cells, ineffective hematopoiesis, increased apoptosis, peripheral blood cytopenia, and risk of progression to acute myeloid leukemia (AML). The recent progress in understanding the pathogenesis of these diseases is due to the emergence of next-generation sequencing (NGS) and the simultaneous interpretation of changes in cell morphologies, cytogenetics, and molecular mutations, which have provided the conditions for better classification and determination of efficient prognosis. Based on the Revised International Prognostic Scoring System (IPSS-R) system, MDS treatment approaches were divided into two groups: low-risk MDS, and high-risk MDS. In low-risk MDS, MDS is not the main cause of death, and most of the patients die as a result of cytopenia and the quality of life. Therefore, the goal of treatment approaches in low-risk MDS is to improve the quality of life in patients. However, in patients with high-risk MDS, the possibility of progression to AML is life-threatening. Therefore, clinical decisions aim to improve the course of the disease.

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1. Introduction

MDS are clonal disorders of hematopoietic stem cells (HSCs) that begin with hypercellularity, dysplasia, ineffective hematopoiesis, and increased apoptosis in the bone marrow that led to peripheral blood cytopenia and progression to AML. Cytogenetic changes, gene mutations, extensive hypermethylation of target genes, and abnormalities of the bone marrow microenvironment are among the main defects in MDS (**Figure 1**) [1-5]. The neoplastic nature of MDS made the WHO 2022 classification call it myelodysplastic neoplasms, which is consistent with MPN terminology [6].

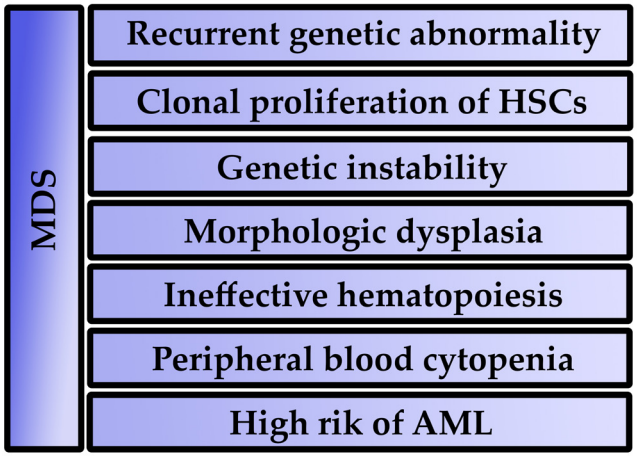

Figure 1: Characteristic of MDS.

The average age of diagnosis is 70 years; however, a small number of patients are diagnosed before the age of 50. The incidence rate of MDS is about 4 cases per 100,000 people per year, but in patients over 70 years old, this rate reaches 40-50 and sometimes up to 70 cases per 100,000 people. Ethnic differences do not affect the incidence of MDS, but in comparison to western populations, it occurs at a younger age in asian populations [1-3].

The main causes of MDS are known in only 15% of cases. Hereditary susceptibility to MDS is seen in one-third of affected children. Although this condition is less observed in adults, in families with a history of MDS, AML, or aplastic anemia cases, hereditary predisposition should be noted. Environmental factors affecting the occurrence of MDS include previous exposure to chemotherapy, radiotherapy or ionizing radiation, and smoking. Known occupational factors include working with benzene and its derivatives. Cases of "secondary MDS," especially treatment-related MDS, generally have a poor prognosis with a complex involvement of chromosomes 5, 7, or 17p [4, 5, 7].

2. Clinical symptoms

Clinical manifestations of MDS are usually non-specific. Patients present with signs and symptoms of cytopenia, fatigue and shortness of breath due to anemia, infections due to neutropenia, or bleeding and bruising due to thrombocytopenia and thrombocytopathy. All these symptoms suggest a diagnostic workup for MDS. In a Swedish study, 42% of recently diagnosed patients had a hemoglobin of 8-10 g/dL, which 50% of them needed red blood cell transfusion, and 40% had a platelet count less than 100 $\times 10^9$/L and 20% had less than 0.8 $\times 10^9$/L neutrophils. The clinical course of MDS is usually stable, but in a group of patients, progression to AML occurs within a short period [3, 8].

3. Diagnosis

MDS is diagnosed based on the examination of peripheral blood and bone marrow. Peripheral blood cytopenia and bone marrow hypercellularity (sometimes hypocellular) with dysplasia with or without increased blasts are characteristic of MDS. Evaluation of peripheral blood cells in terms of the count and morphology and their differentiation statue as well as the bone marrow smear and cytogenetic analysis are the available tools which can be used to the diagnosis of MDS.

To exclude other causes of cytopenia and to provide prognostic information, bone marrow histology is strongly recommended at the time of diagnosis. Molecular studies with NGS to check clonality and flow cytometric evaluations of peripheral blood and bone marrow cells that provide co-criteria for diagnosing MDS can be useful for difficult diagnosing cases (**Figure 2**) [9, 10]. Dysplasia in ≥10% of major bone marrow cells (erythroid, granulocyte, or megakaryocyte) or peripheral blood cells is a cytomorphological hallmark in MDS [11, 12]. Clonal chromosomal abnormalities are observed in many patients with MDS (from 30 to more than 80 percent of cases). In those with normal karyotype, sub-microscopic changes such as point mutations, amplifications, microdeletions, copy number neutral loss, and epigenetic changes provide the genetic basis of the disease [13-19]. In an international database, 1105 of 2124 patients with MDS (52%) showed one or more clonal chromosomal abnormalities. Abnormal karyotype was significantly related to MDS severity, dysplasia severity, and increased number of blasts in the bone marrow. Several studies proved the adverse outcomes associated with complex genetic abnormalities, such as the presence or absence of TP53 mutations and the number of cytogenetic changes [16, 20, 21]. MDS patients with adverse karyotypes show less and shorter complete remission than patients with normal karyotypes. Therefore, karyotype examination is helpful not only at the time of diagnosis but also during the follow-up of patients because the deterioration of the cytogenetic status or the improvement of the cytogenetic response

are associated with a weaker prognosis or an appropriate response to treatment, respectively [21-23]. Molecular mutations are seen in 80 to 90% of MDS patients in an acquired form, which affect transcription, signal transduction, splicing and epigenetic regulation, and chromatin remodeling and cause clonal involvement, **Table 1**. The most common mutations affect SF3B1, TET2T, ASXL1, SRSF2, RUNX1, and DNMT3A genes. About half of the patients with MDS have more than one mutation, and most of the mutations are associated with poor prognoses [24, 25].

4. Differential diagnoses

In order to make a differential diagnoses of MDS, it is important to exclude other diseases such as Aplastic Anemia (AA), Iron Deficiency Anemia (IDA), Hemolytic Anemia (HA), Megaloblastic Anemia (MA), Congenital Dysplastic Anemia (CDA), anemias of kidney disease, Paroxysmal Nocturnal Hemoglobinuria (PNH), chronic infections, kidney failure, autoimmune disorders, and Immune Thrombocytopenic Purpura (ITP), toxic bone marrow

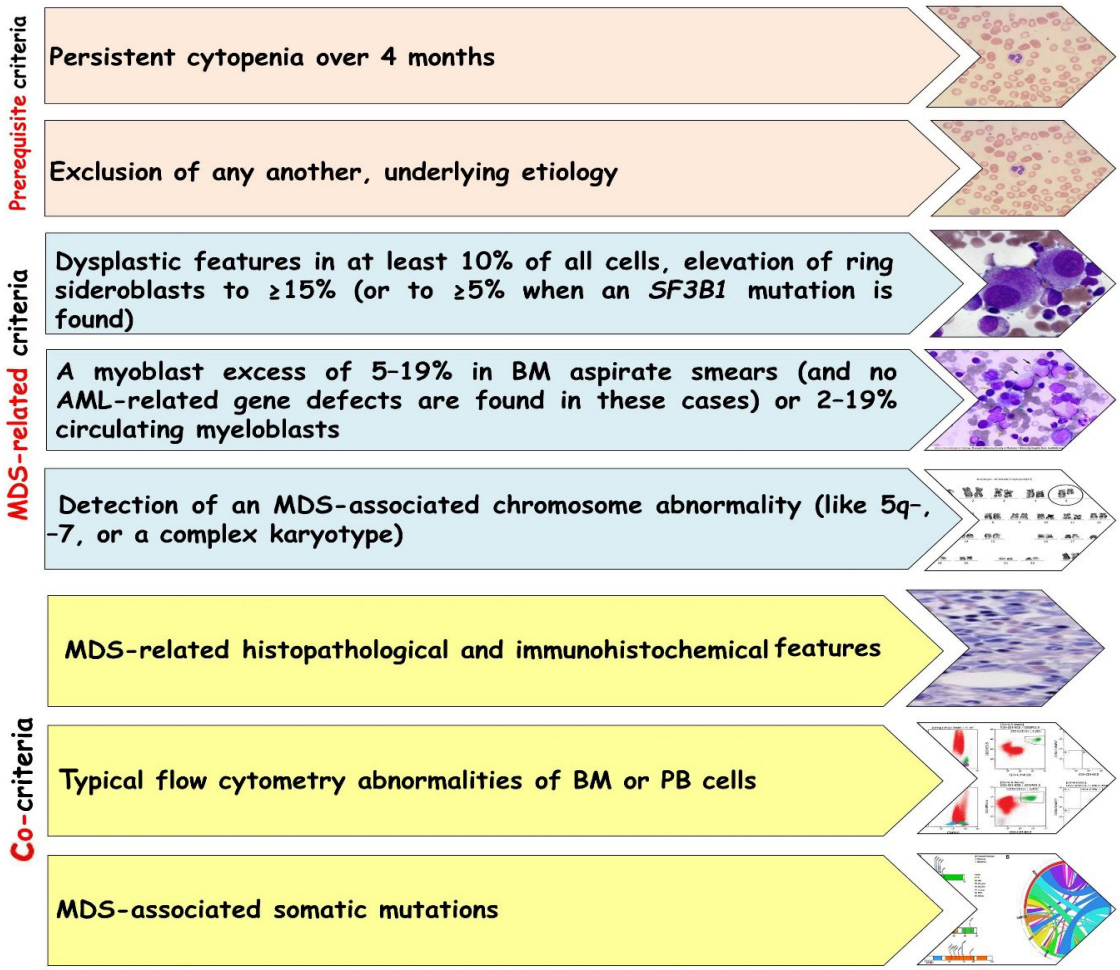

Figure 2. Minimal criteria for diagnosing MDS. Any degree of cytopenia, even mild cytopenia, is considered a prerequisite criterion for MDS, provided that it should be persistent and unexplained. The presence of both prerequisite criteria is necessary for the diagnosis of MDS. At least one of these major MDS-related criteria should be fulfilled (together with the 2 prerequisite criteria) to establish a diagnosis of MDS. When the patient exhibits typical clinical features (e.g., substantial macrocytic anemia) but MDS-related criteria are not met, MDS can still be considered as a (provisional) diagnosis when MDS co-criteria are fulfilled [16].

Table 1: The most common mutations in MDS.

Affected Gene	Gene function
DNMT3A, TET2, IDH1/2	DNA methylation
ASXL1, EZH2, ATRX	Chromatin remodeling
STAG2	Cohesin complex formation
SF3B1, SRSF2, U2AF1/2	Pre mRNA splicing
RUNX1, TP53	Transcription
NRAS, KRAS	Signaling pathway

The most common mutations occur in SF3B1, TET2, ASXL1, SRSF2, and RUNX1 genes. The mutation frequency in SF3B1 gene is 15-30%, TET2, 15-25%, ASXL1, 10-20%, and SRSF2 and RUNX1, 10-15% (30, 31)

damage, bone marrow reactive changes, acute and chronic malignancies and pre MDS conditions, **(Table 2)** [26]. Important laboratory parameters in differentiating MDS from the above-mentioned conditions include the evaluation of ferritin, transferrin and its saturation percentage, vitamin B12 and folate concentration, reticulocyte count, haptoglobin, and creatinine levels.

Table 2: Cytopenic/dysplastic conditions

Aplastic anemia
Metastatic carcinoma
Toxic bone marrow injury
Reactive bone marrow changes
Paroxysmal nocturnal hemoglobinuria
Immune thrombocytopenic purpura
Acute leukemia
Megaloblastic anemia
Hyper splenic syndromes
Myeloproliferative disorder
Congenital dyserythropoietic anemia
Hairy cell leukemia
Idiopathic cytopenia of undetermined significance
Idiopathic dysplasia of undetermined significance
Clonal cytopenia of undetermined significance

5. Classification system

5.1. MDS

MDS was initially described as "preleukemia" in 1953. After that, several terms were proposed to describe this entity. In 1982, the French–American–British (FAB) morphological group proposed a consensus approach for grouping patients. In this classification, MDS was proposed as an independent entity from AML, because the percentage of blasts were increased in MDS, but the patients did not meet the diagnostic criteria of AML. In 2001, the WHO proposed another classification for MDS based on bone marrow morphology and cytogenetics which was subsequently updated in 2008, 2016 and 2022 [26, 27]. The fifth edition of the WHO 2022 classification has been published in LEUKEMIA and has reorganized the MDS grouping with emphasis on histological features and genetic variables. The diagnostic criteria for MDS with low blasts and isolated del(5q) (MDS-5q) have not changed. MDS with biallelic TP53 inactivation (MDS-biTP53) has been introduced as a new subtype. Moreover, MDS with ring sideroblasts (MDS-RS) which is associated with the presence of SF3B1 mutation and low blasts has been replaced by MDS-SF3B1. The cutoff between MDS with low blasts (MDS-LB) and MDS with increased blasts (MDS-IB) has been maintained. Individuals without an increase in the number of blasts are divided into two subgroups: hypoplastic MDS (MDS-h) and MDS-LB. Patients with increased blast count are divided into MDS-IB1, MDS-IB2 and MDS with fibrosis (MDS-f) groups, (Table 4) [6]. The main criteria for diagnosis of MDS are persistent cytopenia in one or more lineage of peripheral blood cells and morphological dysplasia in one or more lineage in bone marrow. Indeed, subtype of MDS are classified based on the number of dysplastic lineages, the presence or absence of the ring sideroblast, the percentage of bone marrow and peripheral blood blasts, and the type of cytogenetic abnormality. Hypoplastic MDS and MDS with fibrosis are not included in the WHO subtypes **(Table 3)**.

5.2. Pre-MDS conditions

During the last two decades, several studies have reported some cases which did not met all of the MDS-related criteria, but some MDS-associated situations

were present. For example, some patients had mild cytopenia with or without dysplasia, or in some other patients, MDS- associated abnormal karyotype was observed, but there was no peripheral blood or bone marrow dysplasia, and cytopenia was either mild or absent. Macrocytic anemia was seen in another group of patients, but MDS-related karyotypes, molecular abnormalities, and dysplasia was not observed. Since, in all these cases, the definitive diagnosis criteria of MDS were not met (**Figure 2**), the term pre-MDS conditions was proposed.

Pre-MDS conditions include idiopathic cytopenia of unknown significance (ICUS), idiopathic dysplasia of unknown significance (IDUS), clonal hematopoiesis of indeterminate potential (CHIP), clonal cytopenia of unknown significance (CCUS). These conditions can be classified based on the presence of cytopenia (ICUS, CCUS) or the absence of cytopenia (IDUS, CHIP) and also based on the presence of the mutation (CHIP, CCUS) or the absence of mutation (ICUS, IDUS) (Figure 3) [28-32].

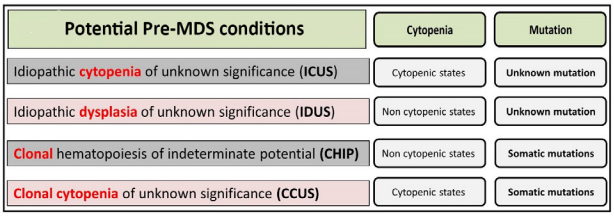

Figure 3. Classification of pre-MDS conditions based on cytopenia status and somatic mutation.

ICUS is a pre-MDS condition in which patient has persistent mild cytopenia (Hb<11.0 g/dl, Neut<1500/μL, Plt<100000/μL) for at least 4 months without any other underlying causes and MDS-related mutations. In IDUS cases, more than 10% of major bone marrow cells (erythroid, neutrophilic, or megakaryocyte) have dysplasia without a clear cause and the patients do not meet a minimum criteria for a definitive diagnosis of MDS. CHIP is another MDS-related condition in which HSCs undergo somatic mutation and achieve Variant allele frequency (VAF ≥ 2) with no significant

Table 3. 2022 Classification of MDS

	Blasts	Cytogenetic	Mutations
A) MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and SF3B1 mutationa (MDS-SF3B1) [a]	<5% BM and <2% PB	Absence of 5q deletion, monosomy 7, or complex karyotype	SF3B1
MDS with biallelic TP53 inactivation (MDS-biTP53)	<20% BM and PB	Usually, complex	Two or more TP53 mutations ,or 1 mutation with evidence of TP53 copy number loss or cnLOH
B) MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoblastic (MDS-h)[b]	<5% BM and <2% PB		
MDS-Increased blast 1	5–9% BM or 2–4% PB		
MDS-Increased blast 2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

a. Detection of ≥15% ring sideroblasts may substitute for SF3B1 mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
b. By definition, ≤25% bone marrow cellularity, age-adjusted.
Abbreviations. BM: bone marrow, PB: peripheral blood, cnLOH: Copy neutral loss of heterozygosity.

cytopenia or dysplasia and minimum criteria for definitive diagnosis of MDS. If somatic mutations with VAF ≥ 2 was along with a mild cytopenia, the condition is termed as CCUS. Summarized definition of pre-MDS conditions is provided in the **Figure. 4** [16].

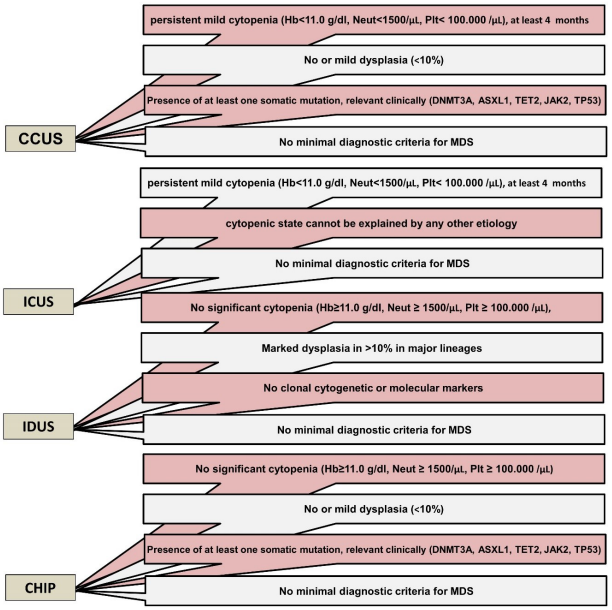

Figure 4. Definition of pre-MDS conditions

The clinical course of patients with pre-MDS conditions is very variable. While a group of patients remains in the same state without any clinical symptoms or progression, other patients recover shortly after the emergence of initial symptoms and some others progress to myeloid and lymphoid hematological neoplasms such as MDS, AML, and lymphomas, or non-hematological disorders such as cardiovascular diseases and atherosclerosis. Therefore, since the clinical course of the patients is not definitively known, appendices undetermined or unknown significance (US) and indeterminate potential (IP) have been used intelligently to prevent overdiagnosis & misdiagnosis ,especially in the elderly, who often suffer from age-related diseases [17, 33, 34]. As a result, follow-up is not required in elderly patients. However, in the case of young patients with CCUS or CHIP, follow-ups should be performed, and progression to MDS or AML should be evaluated. Taken together, it is recommended to treat pre-MDS patients similarly to lower-risk MDS patients [16, 17, 32, 33].

6. Risk evaluation

The clinical course of MDS and the survival of patients are variable in different subgroups. while most of the patients with lower-risk MDS die for other reasons, the main cause of death for patients in the higher-risk group is MDS or progression to AML. In some cases, pre-abnormalities in the microenvironment of the bone marrow led to the infection and bleeding before progressing to AML, infection, and bleeding resulting from cause the death of patients [35, 36]. The number of dysplastic lineage and the severity of cytopenia, the percentage of blast in bone marrow, and cytogenetic abnormalities are among the main risk factors considered when adopting a personalized treatment strategy [1]. The IPSS-R prognostic system classifies MDS patients into five risk groups (very low risk, low risk, moderate risk, high risk, and very high risk) with significantly different probabilities of progression to AML and Overall survival (OS) **(Table 4)** [18]. Treatment approaches divide MDS patients into two groups: low-risk MDS and high-risk MDS. While the term low-risk MDS is generally used in cases where patients have scored IPSS-R <3.5, High-risk MDS patients score ≥4.0 from the IPSS-R classification. Since there are uncertainties in the management of patients with moderate risk other risk factors such as the age of involvement, comorbidities, functional status, multilevel dysplasia, transfusion of red blood cells, serum LDH, the profile of somatic mutations and their number, bone marrow fibrosis, as well as flow cytometry immunophenotyping data should be considered for the treatment of this patients [37, 38].

7. Treatment

The goal of treatment strategies in MDS patient is to improve the patients survival and their quality of life. Patients' responses should be regularly evaluated in terms the improvement of cytopenia (hematological improvement) and disease progression [39]. The most frequent treatment strategies are Hypomethylating agents (HMAs), severe or mild chemotherapy, allogenic bone marrow transplantation (BMT), Erythropoiesis Stimulating Agents (ESAs), immunomodulating agents and repeated RBC transfusions **(Figure 5)** [40]. There is not enough information about the effects of somatic mutations in the adoption of therapeutic strategies. Currently, some clinical studies are ongoing

Table 4: IPSS-R prognostic score values and their associated Overall survival in 7012 patient

Risk category	Risk score	Percentage in total patients	Overall Survival***	Progression to AML***
Very Low	<=1.5	19%	8.8	NR
Low	>1.5 - 3	38%	5.3	10.8
Intermediate	>3 - 4.5	20%	3.0	3.2
High	>4.5 - 6	13%	1.6	1.4
Very High	>6	10%	0.8	0.7

***Medians, years ^Median time to 25% AML evolution

for evaluation the effects of some inhibitors which mainly target MDS-related mutations such as TP53, SF3B1, and IDH1/2 [41].

7.1. Treatment of high-risk MDS patients

Since there is a possibility of progression to AML and a poor overall survival, the goal of the treatment is to modify the course of the disease. Hypomethylating agents (HMAs), AML-like intense Chemotherapy and allogenic stem cell transplantation are the most important treatment strategies in this area.

7.1.1. Hypomethylating agents (HMAs)

Hypomethylating agents are a group of epigenetic regulators which are currently approved for the treatment of MDS and AML. Valuable results of azacytidine, as one of the most common HMA, has been stablished by the results of previous studies in both AML and high-risk MDS patients. High-risk MDS patients usually respond to at least six courses of azacytidine. Typically, 75 mg/m2/day is administrated subcutaneously for 7 consecutive days every 28 days and 2-2-5 regimens (from Monday to Friday/Monday and Tuesday of the following week) are more popular due to their ease of use. In order to have enough time to find a suitable donor for BMT and to reduce the number of blasts in the bone marrow, it is common to administer 2 to 6 courses of azacytidine before transplantation. Usually, Patients who do not respond to azacytidine and are not eligible for allogenic BMT have a very poor survival (median survival less than 6 months). Combination of some small molecule inhibitors such as Venetoclax (Bcl2 inhibitor), which was approved for AML patients, is being investigated in higher-risk MDS patients [42-44]. Moreover, efficacy of Ivosidenib and enasidenib, which are IDH1 and IDH2 inhibitors, respectively, has been proven in the treatment of AML and their potential application in high risk MDS patients is under investigation [45, 46]. Currently, studies are investigating new HMAs with increased hypomethylation effect and longer half-life [47, 48].

7.1.2. AML-like intense Chemotherapy

Efficacy AML-like intense chemotherapy in high-risk MDS patients has been proved by the results of clinical studies [49]. For instance, a combination of cytarabine with idarubicin or fludarabine is successful before allogenic BMT in eligible patients younger than 70 years which have more than 10% blasts in the bone marrow and normal karyotype. Taken together the superiority of HMA on the survival of MDS patients comparing to AML-like chemotherapy was reported without a statistically significant difference. The new encapsulated form of daunorubicin and cytarabine, CPX 351, has shown favorable effects in AML patients with MDS features. However, whether it is superior to normal chemotherapy in high-risk MDS has not been determined [50-52]. In addition, it has been reported that administration of low-dose chemotherapy or LDAC in the form of cytarabine (20 mg/m2/day for 10-14 days/4 weeks) in high-risk MDS patients with abnormal karyotype has poorer results in terms of response to treatment and survival when compared to azacitidine [52-54].

7.1.3. Allogenic-BMT

Based on the fact that the majority of individuals with MDS are of older age, BMT is not recommended in majority of MDS cases. However, Allogenic-BMT is one of the major therapeutical options in younger patients (≥70 years) and the possibility of that should be evaluated at the time of diagnosis and during the course of the disease if necessary (**Figure 5**). In addition to age, comorbidity, IPSS-R score, mutations,

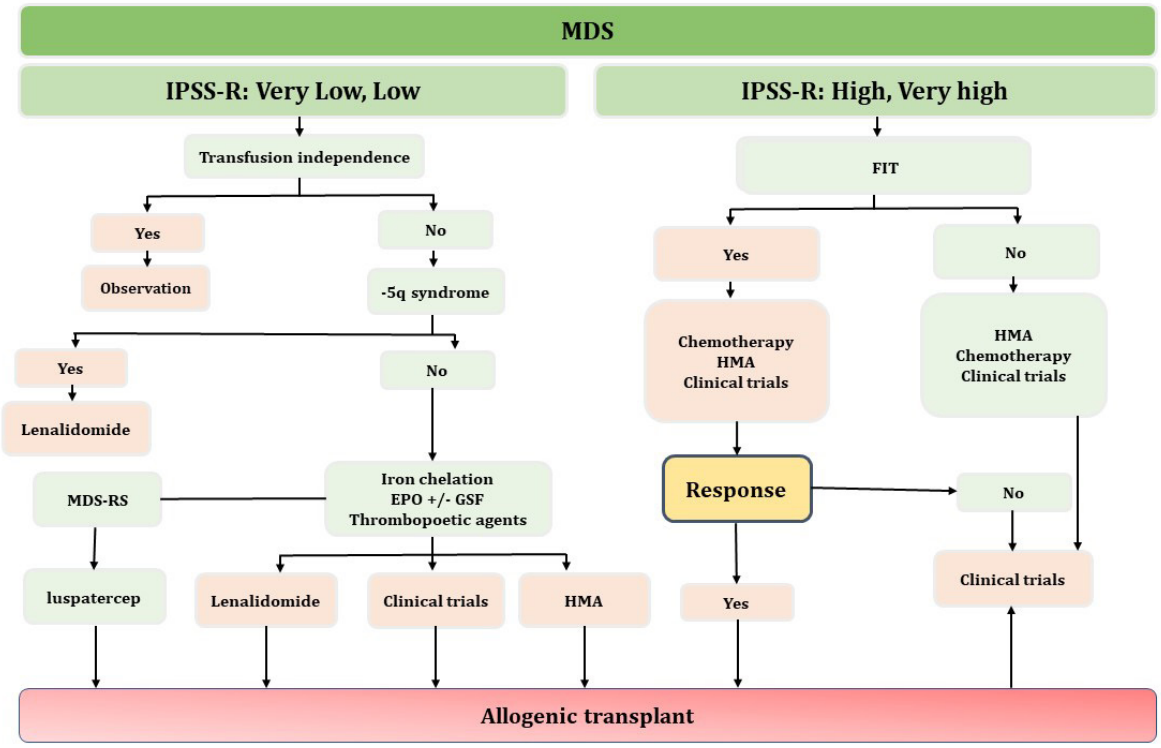

Figure 5: Treatment approaches of MDS. MDS: myelodysplastic syndrome; int: intermediate; MDS-RS: a myelodysplastic syndrome with ring sideroblast; EPO: erythropoietin; HMA: hypomethylating agents

cytogenetics, and the type of conditioning regimen (RIC or myeloablative) are determinants of transplant outcome and must be considered [55-57]. Moreover, transfusion-associated Iron overload is an adverse prognostic factor for patients undergoing allogenic-BMT and it is accompanying with an increase in infection-related mortality and a robust decrease in overall survival of the patients with AML or MDS. Therefore, it is necessary to prescribe appropriate iron chelators for eligible patients to prevent from iron deposition before allogenic-BMT [58, 59].

7.2. Treatment of low-risk MDS patients

In low-risk MDS patients, the goal of the treatment policies is to correction of cytopenia and reducing blood product support, reduce transfusion needs, improving quality of life, and maintaining it, prolong overall survival, and maybe reduce the risk of progression to leukemia **(Figure 5)** [60].

7.2.1. Treatment of anemia

Repeated RBC transfusions can be considered the only treatment strategy for anemia in low-risk MDS and although many important steps have been taken to date, no oxygen-carrying blood substitutes are approved. Frequent RBC transfusion leads to undesirable side effects such as iron-overload and subsequent negative impacts on various organs of the body which can affect the quality of life in patients. Currently, utilizing Erythropoiesis-stimulating agents (ESAs), such as recombinant human erythropoietin (EPO), have achieved promising results in the correction of anemia in MDS patients without transfusion-associated side effects **(Figure 5)** [60-66]. The first line of treatment for anemia in most patients with lower-risk MDS without del (5q) is recombinant EPO or darbepoetin (DAR). In patients with no or limited need for blood transfusion, low doses of 30,000 to 80,000 units of EPO or 150-300 µg of DAR produced a 50% erythroid response and addition of granulocyte colony stimulating factor (G-CSF) improve this response **(Figure 5)**. Notably, 8-12 weeks to respond to ESA, and the average response time is 20-24 months [62, 64-66, 68-70].

In patients with del(5q), the average response to ESA is shorter than MDS patients who do not have this cytogenetic abnormality. However, 65% of patients respond to an initial dose of 10 mg/day lenalidomide for 3 weeks every 4 weeks and experience a cytogenetic response in 75% of patients **(Figure 5)**. Concurrent

TP53 mutation in the low-risk MDS patients with del(5q) lead to a resistance against lenalidomide and also an increased risk of progression to AML which highlight the demand for regular examination of the bone marrow in the these patients. However, the response to treatment in those low-risk MDS patients with del(5q) who have other chromosomal abnormalities is similar to the patients with single del(5q) [71-75]. Regular monitoring the complete blood cell count to check the number of neutrophils and platelets in the first weeks of treatment is highly recommended because neutropenia and thrombocytopenia are the most common complications of lenalidomide [57]. Repeated RBC transfusion is the only treatment strategy for anemia correction in low-risk MDS patients without del(5q) who have primary or secondary resistance to ESAs is. Second-line treatment options for correction of anemia include lenalidomide, anti-thymocyte globulin (ATG), and HMAs. Administration of ATG with or without cyclosporine can produce an erythroid-platelet response in less than half of patients under the age of 65 with thrombocytopenia, normal cytogenetics, no additional blasts, and with hypocellular bone marrow and a history of recent blood transfusion [76-80]. Lenalidomide induced independency to RBC transfusion in less than half of ESA-resistant low-risk MDS patients without del(5q), and studies have shown that its combination with ESAs increases the rate of RBC transfusion independency. Recently, the administration of Luspatercept (ACE-536) in RBC transfusion-dependent low-risk MDS (very low-risk and low-risk IPSS-R) patients, especially patients with SF3B1 mutations or those with intermediate-risk MDS-RS, showed an enhanced erythroid response [81-85]. Failure in response to low-risk MDS with del(5q) or mutation in the TP53 gene is associated with poor prognosis and adverse outcomes, making patients candidates for treatments such as HMAs and Allogenic-BMT, which have improved survival in high-risk MDS [71, 83].

7.2.2. Treatment of neutropenia and thrombocytopenia

In low-risk MDS, isolated or severe neutropenia and thrombocytopenia rarely occur. Neutropenia defined as less than 1500/mm3 is seen in a small number of low-risk MDS and is rarely life-threatening. G-CSF can improve the neutrophils in 75% of patients and it can be added to anti-infective drugs [3]. Platelets less than 50,000/mm3 are seen in about one-third of low-risk MDS cases. High-dose androgens can transiently improve thrombocytopenia in 30% of patients. A dose of 500-1000 micrograms per week (high dose) of Romiplostim, a thrombopoietin receptor agonist, has improved platelet counts by 55% in patients with lower-risk MDS. Of course, complications such as increased blasts in the peripheral blood and bone marrow have been observed in a small number of patients. Studies have shown that this drug can significantly decrease the need for platelet transfusions and severe bleeding manifestations. Eltrombopag, a novel second-generation thrombopoietin receptor, has also shown a 50% platelet response with reduced bleeding manifestations [85-89]. Administration of ATG with or without cyclosporine/HMA has improved platelet responses in addition to erythroid responses in less than half of low-risk MDS cases [76-78].

8. Supportive treatments

Generally, MDS patients also need supportive care during their disease. Their hemoglobin should be kept within the upper limit. Therefore, to limit the effects of chronic anemia on the quality of life, it is necessary to administer a sufficient number of RBC concentrates within 2 to 3 days. Prophylactic transfusion of platelets and antibiotics is usually not recommended. In the case of neutropenia, G-CSF is not suggested. However, as soon as the symptoms of infection appear, the administration of broad-spectrum antibiotics is mandatory, and G-CSF has shown favorable effects in this regard. The harmful effects of iron overload in MDS patients have not been definitively determined because many patients have other reasons for their cardiovascular disorders besides MDS complications. However, various studies have demonstrated iron overload during administration of at least 70 RBC concentrates. Chelation regimen significantly improved the survival of patients and the function of heart, liver, and kidney systems and it is suggested to administer these agents, when serum ferritin is greater than 1000-2500 U/L. Iron chelation for allogenic-BMT candidates should be performed in MDS patients before transplantation to avoid iron overload causing post-transplant mortality [58, 59, 75, 91-93].

9. Monitoring

MDS patients are mainly monitored through complete blood cell counts so that necessary measures

such as blood transfusions or rapid administration of broad-spectrum antibiotics can be taken in the case of severe cytopenias. In the case of progressive cytopenias or the appearance of blasts in the peripheral blood, the bone marrow should also be evaluated [57]. Progression of MDS to AML is relatively common, and regular follow-up, such as bone marrow cytogenetic evaluation, is mandatory for all MDS patients. The follow-up time frame of patients depends on their risk classification and response to treatment. AML secondary to MDS is called AML with myelodysplastic changes [13, 94].

10. Minimum residual disease (MRD)

With the advent of combination therapies associated with high rates of response and remission, approaches derived from MRD assessment have become an attractive treatment strategy for patients with higher-risk MDS. For example, if the disease relapses after allogenic-BMT, the treatment at the time of molecular relapse will be more effective than hematological relapse. Therefore, early detection can be achieved by regular monitoring of MRD. Sensitive techniques of MRD evaluation, such as NGS and multi-color flow cytometry, which have a high rate of accuracy and specificity, can determine the clonal and sub-clonal status of the disease and detect the disease recurrence as soon as possible. Different mutations with prognostic significance should be evaluated in all stages of treatment course. However, it is not yet clear whether they can be used as a marker in MRD evaluation before or after allogenic-BMT.

For example, mutations in genes such as IDH2, TET2, TP53, RAS, and DNMT3A are associated with poor outcomes. However, more research is needed to determine how these genes can be used for MRD screening [94-96]. Taken together, genotypic and phenotypic heterogeneity of MDS has made it impossible to find unique markers to evaluate MRD for all patients. Therefore, the smart solution is to make individual evaluations based on the NGS panel for each patient. In this regard, it was reported that the expression level of WT1 can predict imminent relapse with high sensitivity and specificity in most MDS patients independently of genotype [98]. In an ongoing clinical trial on MDS patients after Allogenic-BMT, individualized molecular MRD monitoring is being investigated to provide high-sensitivity strategies based on each patient's unique panel of mutations for early detection of relapse (NCT02872662).

11. Conclusion

Recent advances in the field of molecular genetics and cytogenetics have improved the understanding of the pathogenesis of MDS. The numerous classifications of MDS and its successive editions are proof of this. The recent classification of WHO 2022 has divided MDS patients into two groups: MDS with defining genetic abnormalities and MDS, morphologically defined. the main purpose of this classification is to pay more attention to the patient's condition and choose the appropriate treatment according to the risk stratification of each patient. Since MDS is incurable in some patients by the first line of treatment, continuous studies are necessary to identify new treatments and this raises the need for personalized medicine.

Conflict of interest

The authors declare that they have no conflict of interest.

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