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Myelodysplastic Neoplasms (MDS)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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- Guideline
- Conflict of interests

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1 Summary

Diagnostics from peripheral blood and cytological and histological bone marrow diagnostics in combination with cytogenetics and molecular genetics represent the current gold standard in MDS diagnostics. Risk scores such as the IPSS-R and the IPSS-M allow an estimation of the prognosis of patients with regard to their overall survival and the risk of progression to acute myeloid leukemia. The mostly advanced age and the frequent comorbidities of the patients, as well as the toxicity of therapy, limited response rates and short remission durations after conventional therapy, represent a challenge for the management of patients with MDS.

The treatment should consider the individual quality of life and longevity, as far as possible. The allogeneic stem cell transplantation is the only curative treatment option, which is applicable only to selected cases over 70 years of age, despite improvements in the field of transplantation. The basis of treatment is supportive therapy, especially basing on the administration of hematopoietic growth factors, erythrocyte concentrates, platelet concentrates and, if necessary, iron chelation. For patients with advanced MDS who are not eligible for allogeneic stem cell transplantation, hypomethylating agents represent an effective and tolerable therapy that is possible on an outpatient basis. There are only a few established drugs in the therapy of MDS. Newer effective substances, such as TPO-R agonists and venetoclax, are only applicable in the context of clinical studies or in off-label status (after individual reimbursement approval by the respective health insurance).

2 Basics

2.1 Definition and basic information

MyeloDysplaStic neoplasms (MDS, the WHO classification 2022 uses the term "myelodysplastic neoplasms" [1], however continues the abbreviation "MDS") are clonal diseases of the hematopoietic stem cell characterized by dysplasia of blood and bone marrow cells associated with hematopoietic insufficiency and increased risk of developing acute myeloid leukemia (AML). Therapy-associated MDS (approx. 10 %) can occur after previous chemotherapy and/or radiotherapy. In approx. 90 % of cases, a noxious agent remains unknown. The prominent finding is usually anemia, often also bi- or pancytopenia. The bone marrow is often normo- or hypercellular, in about 10% of cases hypocellular. Dysplasia signs of one or more cell rows are diagnostically indicative. It is mandatory that at least 10 % of the cells of one cell row must show clear signs of dysplasia.

2.2 Epidemiology

MDS are among the most common malignant hematologic disorders, with an incidence of approximately 4-5/100,000 inhabitants per year [2]. At ages older than 70 years, the incidence increases to >30/100,000. The median age of onset is approximately 75 years, and women are affected slightly less frequently than men.

2.3 Pathogenesis

The pathogenesis of MDS represents a complex process in which a gradual accumulation of genomic damage (DNA mutations) and epigenetic changes in hematopoietic stem cells is assumed to be causative. It is assumed that this leads to a selection of malignant stem cells, which increasingly colonize the bone marrow with their progenitor cells and displace the healthy hematopoiesis. In the last decade, the availability of high-throughput molecular methods has identified numerous new molecular lesions that are recurrent but not exclusive in MDS. In approximately 50% of MDS chromosomal alterations are seen. Other mutations are mainly point mutations, which were detected in genes of the splicing apparatus (e.g., *SF3B1, SRSF2, ZRSR2, U2AF1, PRPF8*), of regulators of epigenetic modifications (e.g. *DNMT3A, TET2, ASXL1, IDH1/2, EZH2, WT1*), of transcription factors (e.g. *RUNX1, TP53, ETV6, GATA2, BCOR, BCORL1, CUX1*), of the cohesin complex (*STAG2, RAD21, SMC3*), of the RAS pathway (*PTPN11, NF1, NRAS, KRAS, CBL*), of cytokine receptors and tyrosine kinases (*CSF3R, FLT3, KIT, MPL*) and others [3]. In approximately 95% of all MDS patients, at least one of the recurrent mutations and/or karyotype alterations is detectable.

In addition to alterations in hematopoietic stem cells, disorders in the bone marrow microenvironment (niche) became apparent in recent years. Initial experimental work has demonstrated that genetic damage in the bone marrow stroma alone may be sufficient to generate an MDS phenotype. Furthermore, xenotransplantation experiments of primary MDS cells in immunodeficient mice demonstrated that hematopoietic cells from MDS patients need bone marrow stroma support for disease maintenance. Here, diseased MDS hematopoiesis apparently exerts an instructive effect on the bone marrow niche, which in turn creates favorable growth conditions for MDS cells [4].

2.4 Risk factors

Several individual factors, alone or in combination, may favor the development of MDS. Etiologically, primary forms of MDS and therapy-associated (secondary) forms are distinguished.

In secondary MDS, the changes in hematopoiesis occur after previous radiation and/or chemotherapy. In particular, treatment with alkylating agents in combination with radiation therapy (e.g., for lymphoma, mammary Ca) is associated with the risk of occurrence of MDS as a secondary neoplasia. The latency period for the appearance of MDS in these cases is on average 2-6 years.

A special form of the disease is MDS following long-term exposure to substances containing benzene or other organic solvents. Typically, affected persons are former service station employees, painters and varnishers, and airport employees (refueling of aircraft with kerosene). The prerequisite for recognition as an occupational disease in these cases is a long-lasting exposure (usually 10-20 years) to the chemicals mentioned.

In connection with the frequent occurrence of leukemia after radiation exposure (atomic bombing in Japan in 1945, reactor accident in Chernobyl in 1986), increased numbers of myeloid neoplasms, which rapidly turned into acute leukemia, were observed. These experiences suggest

that high radiation exposure causes changes in hematopoiesis that may lead to the development of MDS.

Diseases that occur without evidence of the factors presented are classified as a primary MDS. In recent years, germline mutations have been identified that are associated with a familial risk of MDS or AML. As the age of onset can be around 60-70 years even with germline mutations (e.g., DDX41 mutation), exploration of family history is important here.

3 Prevention and early detection

3.1 Prevention

Due to the lack of clear associations between certain pathogenic noxae and the development of MDS, no effective preventive measures are available. Compliance with occupational health and safety regulations when handling chemicals and radioactive radiation are part of primary prophylaxis.

3.2 Early detection and early disease

Potential early forms of MDS are classified depending on the presence of cytopenias and cytogenetic or molecular alterations (Table 1) [1, 5]. These subgroups have in common that they do not (yet) fulfill the criteria of MDS.

ICUS (idiopathic cytopenia of undetermined significance) is defined by cytopenia and by the absence of molecular or cytogenetic aberrations.

In **IDUS** (idiopathic dysplasia of undetermined significance), only dysplastic changes in the bone marrow can be detected.

In **CHIP** (clonal hematopoiesis of indeterminate potential), molecular mutations can be detected, and DNMT3A, TET2, ASXL1 and splicing factors are mainly affected [6, 7]. However, cytopenia is not present. Per se, these are benign changes found mainly in the elderly. Clinically, the risk of developing manifest MDS or other malignant hematologic disease is significantly increased. Furthermore, mortality is increased (compared to reference populations) due to non-hematologic causes such as cardio-vascular complications.

In **CCUS** (clonal cytopenia of undetermined significance), cytopenia is present in addition to molecular aberrations. CCUS has been defined as a new entity in the WHO and ICC classifications [1, 5]. Depending on the individual disease course, control examinations are recommended approximately every 3-6 months, especially in the presence of molecular mutations.

Table 1: Classification of early forms of MDS.

					MDS		
	ICUS[1]	**CCUS[2]**	**IDUS[3]**	**CHIP[4]**	**Low risk**	**High risk**	
Cytopenia[5]	+	+	-	-	+	+	
Dysplasia	-	-	+	-	+	+	
KM blasts	<5 %	<5 %	<5 %	<5 %	<5 %	≥5 %	
Cytogenetic changes	±	±	±	±	+	++	
Molecular genetic alterations	-	+	-	+	+	+++	
Comment	Cytopenia		No cytopenia		According to WHO classification		

Legend:
[1] idiopathic cytopenia of undetermined significance
[2] clonal cytopenia of undetermined significance
[3] idiopathic dysplasia of undetermined significance
[4] clonal hematopoiesis of indeterminate potential
[5] hemoglobin <12 g/dl; absolute neutrophil count <1.8 /nl; platelet count <150 /nl

4 Clinical course

The most frequent initial manifestation in MDS is anemia (in approx. 70-80%), which is often noticed during a routine examination (e.g. blood count check before planned surgery, check by the general practitioner) [7]. In a relevant proportion of patients, the anemia leads to a reduction in quality of life and activity status and often necessitates the transfusion of red blood cell (RBC) concentrates. A proportion of patients presents with the typical symptoms of anemia such as dyspnea, especially on exertion, general physical weakness, palpitations, and headache. Symptoms of cardiac or cerebrovascular insufficiency or coronary artery disease may be exacerbated. If the anemia develops rapidly, visual disturbances or confusion may occur. Clinical findings include pallor of the mucous membranes (hemoglobin (Hb) usually below 10 g/dL) and nail bed (Hb usually below 8 g/dL). Non-specific complaints such as loss of appetite, gastrointestinal symptoms and fatigue are frequent, but the extent of these complaints often does not correlate with the Hb level. About one third of patients reports recurrent infections, especially of the bronchial system or the skin caused by the neutropenia or the dysfunction of the neutrophil granulocytes.

Despite the fact that about 50% of patients have thrombocytopenia at first diagnosis, initial bleeding complications are rare. Petechiae, gingival bleeding or hematomas after minor trauma may develop. In 10% of cases of MDS, the disease manifests with severe hemorrhage, for example of the gastrointestinal tract, the urinary tract, the retina, or the central nervous system.

Rarely, MDS are associated with skin symptoms, especially with acute neutrophilic dermatitis (Sweet syndrome). In CMML, skin infiltration by myelomonocytic cells occurs occasionally. Autoimmunologic manifestations such as arthritis, osteochondritis, or vasculitis (Sweet syndrome) are found in a smaller proportion of patients with MDS, more commonly with CMML, and suggest possible autoimmune phenomena.

5 Diagnosis

5.1 Diagnostic criteria

After exclusion of numerous differential diagnoses (see chapter 5.6), MDS diagnostics include the preparation of a blood count, differential blood count and a bone marrow examination (see chapter 5.2).

5.2 Diagnostics

The required diagnostics are shown in Table 2. The focus is on the cytomorphology of the blood and bone marrow including iron staining. (Examples in eLCH - eLearning Curriculum Hematology for bone marrow cytology using virtual microscopy; https://ehaematology.com/). Morphologically, it is important to determine the peripheral and medullary blast counts as exact as possible. According to the the IPSS-R [8], an exact determination of the medullary blast percentage is of high prognostic relevance (0-2% vs. 3-4% vs. 5-9% vs. 10-19%). It is also obligatory to determine whether the signs of dysplasia affect only one cell line or whether 2 or 3 cell lines are affected. These parameters allow classification into one of the WHO types [1]. In addition to cytology, bone marrow histology is also obligatory because it enables to assess changes of the bone marrow architecture, as well as bone marrow cellularity and fibrosis.

Table 2: Diagnostics

Peripheral blood	Bone marrow
Blood count	Cytology with iron staining
Reticulocytes	Cytogenetics 25 metaphases, if necessary with FISH (chromosomes 5, 7, 8 and others, if necessary)
Differential blood count	Histology
Serum LDH	Immunophenotyping (not mandatory)
Serum ferritin	Mutation analysis diagnostic SF3B1 and TP53; also other high-risk mutations prognostically useful (see IPSS-M, chapter 5.4.1.2)
Serum erythropoietin level	
Folic acid, vitamin B12 in serum	
Blood group	
If applicable, HLA typing and CMV status	

Immunophenotyping is becoming increasingly important as a tool to estimate the blast percentage and to show signs of dysplasia. However, the validity of this method in routine should not be overestimated. In clinical practice, immunophenotyping is used in particular to exclude differential diagnoses.

5.3 Classification

The types traditionally assigned to MDS are separated into two major groups in the current WHO classification (Table 3). In addition to pure MDS, a group of mixed myelodysplastic-myeloproliferative neoplasms is defined. The blast percentage discriminating from acute leukemia is 20% in blood and bone marrow. However, the prognostic score for MDS (IPSS-R; which was mandatory until 2022), still includes patients with up to 30% blasts [8]. Chromosomal analysis and screening for somatic mutations is essential for a clear diagnosis and treatment decision in MDS, as this is the only way to determine the patient's prognosis as exact as possible.

The 2022 WHO classification proposals are based on a new principle, namely the classification of MDS into morphologically defined and genetically defined types [1]. In addition, three new MDS types were defined as distinct entities for the first time. Other types are adopted unchanged from the old WHO classifications. Peripheral cell counts now have less weight in the classification.

Table 3: Classification of MDS according to WHO 2022 proposals [1].

	Blast percentage	Cytogenetics	Mutations
Genetically defined MDS			
MDS with low blasts and isolated deletion (5q).	<5 % KM <2 % blood	Deletion (5q) isolated or with 1 other abnormality except monosomy 7 or deletion (7q).	*SF3B1, TP53 possible* **2 subtypes** a) MDS del(5q) with monoallelic *TP53* mutation b) MDS del(5q) with SF3B1 mutation
MDS with low blasts and *SF3B1* mutation[1]	<5 % bone marrow <2 % blood	No deletion (5q), no monosomy 7, no complex aberrant karyotype	*SF3B1*
MDS with bi-allelic *TP53* inactivation.	any	Typically highly complex aberrant with >3 aberrations	2 or more *TP53* mutations or 1 mutation + copy number loss of *TP53*.[5]
Morphologically defined MDS[2]			
MDS with low blasts			
MDS with low blasts[3]	<5% bone marrow <2% blood		
MDS, hypoplastic[4]	<5% bone marrow <2% blood		
MDS with elevated blasts			
MDS with elevated blasts -1	5-9% bone marrow, and/or 2-4% blood		
MDS with elevated blasts -2	10-19% bone marrow and/or 5-19% blood		
MDS with fibrosis	5-19% KM, and/or 5-19% blood		

Legend:
[1] Detection of ≥15% ring sideroblasts can substitute for detection of SF3B1 mutation.
[2] ≥10% dysplasia sign in at least one cell line.
[3] 2 types: MDS with low blasts and single lineage dysplasia (MDS-0-SLD); MDS with low blasts and multi-lineage dysplasia (MDS-0-MLD).
[4] ≤25% histologic bone marrow cellularity, age-adjusted.
[5] Copy number loss either cytogenetic (17p deletion detectable by banding analysis or FISH) or copy number-neutral loss of heterozygosity (detectable by array analyses or spec NGS techniques). A VAF of 50% or higher is also associated with a high probability of biallelic TP53 inactivation.

In the group of morphologically defined MDS, two entirely new types have been defined in which no association with genetic characteristics is known so far. Both entities can only be diagnosed by bone marrow histology. In MDS with fibrosis, marrow fibrosis grade 2-3 and blast proliferation are present. Hypoplastic MDS is characterized by bone marrow cellularity of (age-adjusted) 25% and no elevated blast count. Estimation of bone marrow cellularity is more reliably with histology than with smear cytology; therefore, in light of these two new entities, histologic evaluation of the bone marrow is now mandatory at diagnosis. The group of MDS without blast proliferation, divided into single-lineage dysplasias and multilineage dysplasias (MDS SLD vs. MDS MLD), has been adopted unchanged from the older WHO classifications. MDS with blast

multiplication also remained the same, except that EB1 and EB2 now became IB1 and IB2, as the term "Excess" was replaced by "Increased".

The definition of MDS del(5q) has been refined, as the presence of a bi-allelic *TP53 mutation* now leads to classification into a prognostically less favorable subgroup. However, a mono-allelic *TP53 mutation* is compatible with this subgroup (MDS del(5q)). In addition, a hierarchy of genetic alterations was agreed upon, as evidence of a del(5q) was prioritized over evidence of an *SF3B1 mutation*, and thus patients with MDS del(5q) and evidence of an *SF3B1 mutation would* not result in classification into the group of MDS with *SF3B1 mutation.* This was done in light of registry data that had shown that neither the clinical nor therapeutic course of patients with MDS del(5q) with or without evidence of ring sideroblasts was distinct. In contrast, patients with *SF3B1 mutation* and 5q deletion showed a significantly less favorable prognosis than patients with *SF3B1 mutation* and intact chromosome 5.

A similar classification has been published by an International Consensus Group (ICC), which differs only slightly from the WHO proposals with regard to MDS. However, the group of MDS with elevated blasts type 2 (bone marrow blasts >9%) is referred to as the MDS/AML category. The MDS with elevated blasts type 2 have a less favorable course compared with the MDS with elevated blasts type 1 (bone marrow blasts <10%) [5].

The genomic landscape MDS is heterogeneous and complex with cytogenetic and molecular components of diagnostic and prognostic relevance. Chromosomal abnormalities may occur in isolation or accompanied by other karyotype changes. The same applies analogously to gene mutations. Chromosomal and molecular abnormalities often occur in combination. In the IPSS-M cohort (n=2,957), 3,186 cytogenetic alterations were detected in 41% of patients and 9,254 oncogenic mutations in 121 genes were detected in 90% of patients. 94% of patients had at least 1 abnormality (median 4). 53% had exclusively molecular mutations, 4% had exclusively karyotype alterations, and 37% had both.

The genes most frequently mutated in MDS [9] include TET2 (30%), ASXL1 (27%), SF3B1 (26%), DNMT3A *(*17%), *SRSF2 (*16%), *RUNX1 (*13%), *TP53 (*12%), *STAG2* and *U2AF1* (9% each), *EZH2, ZRSR2* and *BCOR* (7-8% each), *CBL (*6%), *IDH2* (5%), *NRAS, CUX1, SETBP1, PHF6* and *NF1* (4% each), *DDX41, KRAS, MLL/KMT2A, IDH1* and *JAK2* (2-3% each).

5.4 Prognostic factors

In addition to age, gender, and comorbidities, disease biology parameters can be used to estimate prognosis. The most important prognostic parameters are the medullary blast percentage, cytogenetic and molecular genetic findings, followed by transfusion requirements, blood cell counts and serum LDH [10, 11].

5.4.1 Risk stratification

5.4.1.1 IPSS-R (International Prognostic Scoring System-Revised)

The IPSS-R [8] remains an important validated prognostic system that can be applied to estimate the individual risk of each case (Table 4). This requires the availability of cytogenetic analysis of the patient's hematopoietic progenitor cells (bone marrow).

Table 4: Definition of the IPSS-R (International Prognostic Scoring System-Revised) [8].

Score points							
	0	**0,5**	**1**	**1,5**	**2**	**3**	**4**
Karyotype	A	-	B	-	C	D	E
Bone marrow blasts (%)	≤2	-	>2-<5	-	5-10	>10	-
Hb value (g/dl)	≥10	-	8-<10	<8	-	-	-
Platelets (/nl)	≥100	50-<100	<50	-	-	-	-
Neutrophil granulocytes (/nl)	≥800	<800	-	-	-	-	-
Risk score			**Points**				
Very Low risk:			≤1,5				
Low risk:			2-3				
Intermediate risk			3,5-4,5				
High risk			5-6				
Very High risk			>6				

Legend:
A: Very good (-Y, del(11q)).
B: Good (Normal, del(5q), del(12p), del(20q), double clone with del(5q) except chr7)
C: Intermediate (del(7q), +8, +19, i(17q), other single or double clones)
D: Poor (-7, inv(3)/t(3q)/del(3q), double clone with -7/del(7q), complex (3 aberrations))
E: Very poor (complex >3 aberrations).

A standardized and multicenter analysis of 359 patients with MDS and complex karyotype could show that within the high-risk patients with additional *TP53 mutation* (55% of patients) show a significantly worse overall survival [12]. (This was the first time that a molecular parameter was also defined as a risk factor).

5.4.1.2 IPSS-M (International Prognostic Scoring System-Molecular)

With the IPSS-molecular (IPSS-M), a prognosis score is now available that comprehensively considers the significance of somatic mutations [13]. The IPSS-M implements the following parameters: medullary blast percentage, platelet count, Hb, cytogenetic risk category according to IPSS-R, 17 molecular genetic variables in 16 genes, and the number of mutated genes from a group of another 15 genes. Thus, the mutation status of a total of 31 genes is included. The score is web-based to calculate (https://mds-risk-model.com) and identifies 6 risk groups that differ substantially in expected median survival probability and transformation risk. The IPSS-M is constructed in such a way that it is very convenient for the user by the above-mentioned link and it also works in the absence of individual parameters. Compared to the IPSS-R, 46% of patients are restratified in the IPSS-M, which represents a significant improvement in prognostic prediction accuracy. The IPSS-M is also applicable to secondary and therapy-associated MDS (Table 5).

Table 5: Prognostic groups using the IPSS-M (International Prognostic Scoring System-Molecular).

IPSS-M risk group	Very Low	Low	Mod. Low	Mod. High	High	Very High
Risk score	≤-1,5	>-1.5 to -0.5	>-0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1,5
LFS (years, median)	10	6	4	2	1	0,7
OAS (years, median)	11	6	5	3	2	1
AML transformation (%)						
-after 1 year	0	2	5	10	14	28
-after 2 years	1	3	9	14	21	39
-after 3 years	3	5	11	19	29	43

For the stratification of MDS patients into low-risk or high-risk category with regard to the required therapy decision (see chapter 6), the IPSS-R remains a reliable prognostic score until the IPSS-M is fully established clinically and validated.

5.5 Monitoring of the course of the disease

MDS are dynamic diseases. All relevant parameters such as blood count, bone marrow morphology, cytogenetics and molecular genetics may change in the natural course of the disease as well as during therapy. This can lead to relevant consequences for the therapy strategy e.g. concerning the decision for an allogeneic stem cell transplantation or therapy renunciation or discontinuation. Thus, in longitudinal studies, karyotype evolution can be expected in up to 30% of patients and molecular evolution in up to 70%, which can massively influence the risk stratification and per se represent an unfavorable prognostic criterion. It is obvious that these data must find their way into a lege artis clinical management with the performance of sequential analyses. This is of great importance, if in the individual case it is to be expected that a risk stratification may change and that therapeutic consequences may result. Relevant analyses in this regard include bone marrow cytology, cytogenetics, and molecular genetics and, in the presence of myelofibrosis, histology. It has been shown that the strategy of initiating these diagnostics only in the case of significant blood count changes leads to a progression often being detected too late to be able to react therapeutically in a target-oriented manner. On the other hand, the value of sequential genetic analyses for therapy monitoring has been demonstrated in clinical trials. Therefore, a prospectively designed diagnostic strategy is recommended if this would have clinical consequences (Table 6).

Table 6: Recommended sequences of diagnostic measures in the course of disease in MDS.

Procedure	Material	Interval
Cytomorphology	Bone marrow	Every 12 months
Cytogenetics	Bone marrow	Every 12 months
FISH (Panel) Analysis	Bone marrow	Every 12 months
Determination of high-risk molecular mutations (such as *TP53*, *ASXL1*, and others) is useful to perform risk stratification and, as a consequence, therapy management according to the new molecular score (IPSS-M).	Bone marrow and peripheral blood	Every 12 months
Follow-up of distinct mutations	Peripheral blood	every 3-6 months

5.6 Differential diagnoses

Table 7: Differential diagnoses of MDS

Differential diagnosis	Diagnostic procedure
Aplastic Anemia, Pure Red Cell Aplasia (PRCA)	Histology, cytology
Toxic KM damage (alcohol, lead, NSAIDs, etc.).	Medical history
Reactive KM changes (sepsis, HIV, chronic infections, TB, autoimmune diseases, etc.).	Cytology, medical history, laboratory
Monocytosis of other genesis	Medical history, laboratory
Paroxysmal nocturnal hemoglobinuria (PNH)	Immunophenotyping
Immune thrombocytopenia	Cytology, medical history, disease course
Megaloblastic anemias	Vitamin B_{12} -/folic acid level
Hypersplenic syndrome	Medical history, clinics, splenomegaly
Acute leukemia (especially erythroleukemia)	Cytology
Myeloproliferative disorders (especially aCML, PMF)	Histology, cytogenetics, molecular genetics
Hairy cell leukemia, LGL	Cytology, immunophenotyping, molecular genetics if necessary
Congenital dyserythropoietic anemias (rare).	Molecular genetics

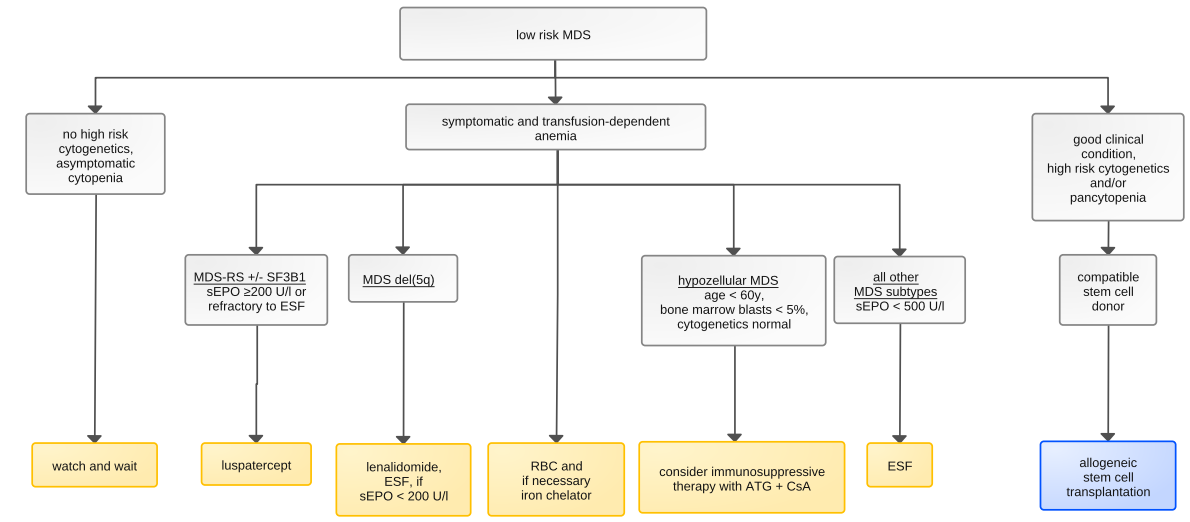
6 Therapy

6.1 Therapy structure

Algorithms for the therapy of patients with myelodysplastic neoplasms are shown in Figure 1 and Figure 3. Whenever possible, patients should be treated in the context of clinical trials.

6.2 Therapy of low-risk MDS (IPSS-R VERY LOW, LOW, and INT).

Figure 1: Therapy for myelodysplastic neoplasms (low risk).



Legend:
palliative, curative.
MDS-RS: MDS with ring sideroblasts; SF3B1+ (positive): Mutation in SF3B1 gene, SF3B1- (negative): no mutation in SF3B1 gene (wild type); sEPO: serum erythropoietin level; ATG: antithymocyte globulin, CsA: cyclosporine. ESF: erythropoiesis stimulating factors.

6.2.1 Indication for therapy (low-risk MDS)

Depending on age and concomitant diseases, a "watch and wait" strategy is initially sufficient in many MDS patients due to low-grade cytopenia. In a significant proportion of cases, however, anemia is the most frequent indication for starting therapy. Anemia leads to fatigue, increased incidence of falls with risk of fracture, decreased cognition and quality of life, and shortened survival, especially in elderly patients.

If therapy is needed, the basis of treatment is a good supportive therapy, including transfusions as well as the administration of antibiotics as needed and the sufficient treatment of concomitant diseases.

The indication for a disease-specific therapy depends on the stage of the disease, age and clinical condition. For most patients, the preservation or improvement of quality of life and autonomy is the main focus of therapeutic efforts. The recommendations of the European Competence Network for Leukemias summarize the therapeutic strategies for patients with MDS depending on the risk classification [14].

The only curative therapy option is allogeneic stem cell transplantation. In general, this form of therapy is reserved for patients with high-risk MDS, but the indication for allogeneic transplantation should also be made in younger patients with low disease risk and severe cytopenia, especially thrombocytopenia with failure on first-line therapy and/or cytogenetic or molecular markers indicating a poor prognosis (e.g. TP53, ASXL1). Here, the application of the IPSS-M will be able to contribute significantly to the treatment decision.

6.2.2 Supportive therapy

The main component of supportive therapy is the transfusion of red blood cell concentrates depending on the clinical condition. In patients with concomitant severe coronary artery disease and/or other severe concomitant diseases, an Hb value above 10 g/dl is the appropriate limit.

Clinically significant bleeding is to be expected above a threshold value of <10 /nl platelets. However, the substitution of platelet concentrates should, if possible, not be done prophylactically (exception: fever, severe infection), but only in case of clinical signs of bleeding (risk of allo-immunization). In each case, the therapy decision must be individually adapted to the circumstances of the patient and the institution providing care (practice, special outpatient clinic with emergency care, etc.). Therapy with tranexamic acid can alleviate bleeding symptoms in the case of severe thrombocytopenia.

Antibiotics should be used generously in case of infections (also minor infections), especially in neutropenic patients. Regular antibiotic prophylaxis is not recommended (so far no clear data for a benefit regarding the number and severity of infections in patients with MDS). However, the general recommendation for vaccination against pneumococci (STIKO recommendation from the age of 65) as well as for influenza vaccination and vaccination against SARS-CoV-2 should be followed.

Adequate treatment of concomitant diseases (lung diseases, heart diseases, etc.) is an important part of the overall therapy.

6.2.3 Iron chelators

Polytransfused patients are threatened in the longer term by concomitant secondary hemochromatosis (cardiomyopathy). Therefore, therapy with iron chelators (deferasirox, desfer-

oxamine) may be considered in patients with a life expectancy of more than 2 years who receive at least 20 red cell concentrates or have a serum ferritin level of >1000 ng/ml [15, 17]. Iron chelation is of particular importance prior to allogeneic stem cell transplantation and is recommended until the onset of conditioning, as iron overload is associated with increased mortality [18, 19].

6.2.4 Hematopoietic growth and differentiation factors

Therapy with erythropoiesis stimulating factors (ESF, classically: subcutaneous erythropoietin 40,000 IU/week, if necessary increase to 80,000 IU/week, once a week if the effect is insufficient; delayed erythropoietin: 300 µg weekly or 500 µg bi-weekly subcutaneously) must follow the so-called "Nordic Score" [20] (Figure 2). Combination with low doses of G-CSF (100 µg G-CSF s. c. 1-2 times per week to modulate the efficacy of ESF, not to raise leukocytes - see above) may improve the effect of ESF, especially in patients with ring sideroblasts refractory to ESF treatment alone.

Taking into account the predictive factors

- Erythropoietin level <200 (500) U/l,
- low transfusion dependency (maximum 2 EC in 8 weeks),
- low risk of disease,

a response can be achieved in up to 75% of appropriately selected patients (Figure 2) [20, 21]. Usually, a response can be expected after 6 months of therapy at the latest. If it does not occur, treatment should be discontinued. A response is possible with an Erythropoietin level of up to 500 U/l.

Figure 2: Modified score of the Nordic MDS Group

The Nordic MDS Group score takes into account transfusion frequency with less than 2 red cell concentrates per month (score value +2) and 2 or more red cell concentrates per month (score value -2) as well as the level of endogenous erythropoietin. Depending on the level of endogenous erythropoietin, a score value of -3 to +2 is assigned. Addition of the score value for transfusion frequency and the score value for endogenous erythropoietin level yields the value that correlates with the likelihood of response to therapy with erythropoiesis-stimulating drugs (ESF

± granulocyte colony-stimulating factor). Early use of ESF may delay the onset of the need for transfusion.

For granulocyte colony stimulating factor (G-CSF), no data from randomized clinical trials justifying its use in MDS are available to date. Treatment with G-CSF may only lead to a transient increase in the number of neutrophil granulocytes. The only accepted exception is interventional G-CSF administration for repeated complicated infections in severe neutropenia.

Inhibition of suppressors of erythropoiesis (poorly characterized to date) in patients with MDS leads to improved differentiation and increased proliferation of erythropoiesis and thus to a reduction of transfusions (particularly in the subgroup of patients with MDS and RS and/or SF3B1 mutation). Luspatercept, an inhibitor of the TGF-beta signaling pathway, is able to achieve a significant reduction in transfusion requirement to transfusion-free in approximately 60% of these transfusion-dependent patents. Patients with MDS-RS (<5% KM blasts, ≥15% ring sideroblasts in KM, or ≥5% ring sideroblasts in KM and mutation of SF3B1) and transfusion-dependent anemia should be treated with luspatercept if they have not responded to ESF or do not have a high probability of response (serum Epo level ≥200 U/l) [22].

The availability of thrombopoietic growth factors (romiplostim, eltrombopag) offers the possibility to successfully treat severe thrombocytopenia in low-risk MDS. Initial results from phase II-III studies suggest that significant improvement in thrombopoiesis associated with a lower incidence of bleeding events can be achieved in 30-50% of patients with platelet counts below 50 / nl [23, 24].

6.2.5 Immunomodulatory and anti-inflammatory substances

Treatment with lenalidomide leads to a response in about 60% of low risk MDS patients with a singular deletion on chromosome 5 and anemia requiring transfusion, resulting in transfusion independence and cytogenetic remission in a proportion of patients. Patients with only one additional aberration (except from chromosome 7) respond similarly well.

The minimum effective dose of lenalidomide has not yet been defined. Based on a randomized trial [25], a dose of 10 mg/day results in a higher rate of cytogenetic remission and should be used-with appropriate adjustment of the dose depending on the platelet count. In older patients, an initial dose of 5 mg/day may be indicated. If there is no improvement in the transfusion requirement after 4 months, therapy should be discontinued. Prior to initiation of therapy, a screening for TP53 mutation should be performed. Patients with a mutation should be monitored regularly for clonal evolution by bone marrow aspirations. The efficacy of lenalidomide in MDS without alterations on chromosome 5 is low. Treatment of these patients with the substance should be strictly weighed [26].

6.2.6 Immunosuppressive therapy

Treatment with immunosuppressive drugs (similar to therapy for severe aplastic anemia) is based on the positive experience in a subgroup of patents characterized as follows [27]:

- hypocellular bone marrow
- MDS with low disease risk
- low need for transfusion

About 30% of patients treated with antithymocyte globulin and cyclosporine achieve freedom from transfusion. Good predictive parameters for response were not identified so far. Because

of the possibly severe side effects and the not yet clearly defined patient population, immunosuppressive treatment in MDS should be performed exclusively at a hematology center.

6.3 Therapy of high-risk MDS (IPSS-R HIGH and VERY-HIGH).

In all patients with high-risk MDS, the option of allogeneic stem cell transplantation should be considered already at diagnosis. Patients who are not eligible for this procedure may receive treatment with azacitidine or decitabine. In case of progression and failure to respond after 4-6 cycles, patients should be enrolled in ongoing clinical trials, if possible (Figure 3).

Further information is available from the German MDS Study Group, the Düsseldorf MDS Registry, and the European MDS Study Office (EMSCO).

Figure 3: Therapy for myelodysplastic neoplasms (high-risk).

Legend:
palliative, curative.
AML: acute myeloid leukemia, allo TX: allogeneic transplantation.

6.3.1 Therapy indication (high-risk MDS)

Since the life expectancy of high-risk patients is significantly limited compared with the age-matched population, there is usually a need for life-prolonging therapy. In addition to supportive therapy, an individual treatment option should be considered for each patient, depending on the disease risk and concomitant diseases.

6.3.2 Intensive chemotherapy

Intensive chemotherapy, analogous to the treatment of AML, is not an established therapeutic option for high-risk MDS patients. Whether intensive chemotherapy is useful in individual cases (e.g., for remission induction prior to planned allogeneic stem cell transplantation) can only be decided on an individual basis, taking into account the risk-benefit ratio. It is certain that patients with an unfavorable karyotype do not benefit from induction chemotherapy unless it is immediately followed by allogeneic stem cell transplantation.

6.3.3 Epigenetic therapy

Azacitidine is a pyrimidine analog that is incorporated into DNA in place of cytosine. This substance has a direct cytotoxic effect on proliferating cells. In addition, it prevents the methylation of CPG segments (so-called CPG islands) in DNA by irreversibly binding and thus inhibiting the enzyme DNA methyltransferase (DNMT).

Azacitidine has been evaluated in several phase II and randomized phase III trials. Treatment with azacitidine in patients with MDS was shown to have an advantage over supportive therapy alone in two independent randomized trials [28, 29]. In both trials, an advantage concerning overall survival of 6-9 months was seen with azacitidine. The difference was statistically significant in the second randomized trial (AZA-001 trial) with the much larger number of cases. In this trial, treatment with azacitidine was superior to standard therapy with supportive care alone or with low-dose cytarabine (low-dose Ara-C) or intensive anthracycline-based chemotherapy in terms of median survival, freedom from transfusion, and improvement in peripheral blood counts.

Patients with high-risk MDS and CMML with <13 /nl leukocytes (dysplastic variant) can be treated with azacitidine if they are not eligible for allogeneic stem cell transplantation (strength of evidence Ib, recommendation grade A). The standard *AZA-7 regimen* is administered subcutaneously or i.v. at 75 mg/m^2 for 7 days. Cycles are repeated at 28-day intervals. Because the effect of epigenetic modulation is slow to occur, at least 4-6 cycles of azacitidine should be administered before response is assessed. Approximately half of patients achieve a response in terms of improvement in peripheral blood counts or remission in the bone marrow. If response is achieved (at least improvement in peripheral blood counts), therapy should be continued until loss of response. It can be assumed that patients who respond will also benefit from the continuation of therapy.

It is also possible to use decitabine, another demethylating agent, which did not prolong overall survival in the initial therapy of patients with high-risk MDS in a prospective randomized study, but can achieve a renewed, transient improvement in hematopoiesis in patients who do not (or no longer) respond to treatment with azacitidine [30]. Patients developing resistance to azacitidine should preferably be included in clinical trials. Combination with venetoclax is another (unapproved) way to treat patients after failure of a demethylating agent and induce renewed hematologic remission. (Inclusion in clinical trials is with venetoclax would be necessary) [31].

6.3.4 Non-intensive chemotherapy

Non-intensive chemotherapy, such as low-dose cytarabine (20 mg/m²/d day 1-14) or low-dose melphalan (2 mg/d), was used in the past in the absence of better alternatives in patients with advanced MDS or was tested in small, mostly phase II trials. With the availability of demethylating agents, the importance of non-intensive chemotherapy for primary therapy of high-risk MDS is receding. Nevertheless, after exhaustion of other options, such as epigenetic therapy, such treatment may well represent a reasonable alternative in individual cases, especially when cytoreduction is required due to high leukocyte counts. Here, especially in MDS/MPN type, therapy with hydroxyurea is indicated.

6.3.5 Allogeneic stem cell transplantation

Allogeneic stem cell transplantation is the only potentially curative approach in the treatment of MDS. With the improvement of supportive measures and a reduction of the intensity of conditioning, it has been possible in recent years to extend the indication to patients over 70 years of age. Nevertheless, this procedure always remains an individualized approach, especially in

patients >65 years of age. Every suitable case with MDS should therefore be presented to a transplant center at diagnosis [32].

7 Rehabilitation

A special rehabilitation measure is usually reserved for younger patients with MDS who have received intensive or curative therapy (allogeneic stem cell transplantation). In most other patients, supportive therapies are the most important measures.

8 Follow-up

In addition to regular blood count monitoring, bone marrow examination is recommended in cases of suspected progression (significant changes in hematopoiesis) or prior to planned curative therapy. In the context of clinical studies and at MDS centers, regular follow-up of bone marrow findings (usually annually) is required (Table 7).

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14 Links

www.mdsdiagnosis.com

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https://d-mds.de/

http://was-ist-mds.de (for patients)

http://www.mds-net-de.org/ (for patients)

https://apps.apple.com/de/app/mds-center/id1277615573 (MDS-APP)

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

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Hofmann, Wolf-Karsten	Land baden-Württemberg	**No**	**No**	**No**	**Yes** Novartis, BMS	**Yes** BMS Phamaxis	**No**	**No**
Passweg, Jakob	Universitätsspital Basel	**No**	**No**	**No**	**No**	**No**	**No**	**No**
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