REVIEW ARTICLE

Myelodysplastic Syndromes: Diagnosis, Prognosis, and Treatment

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SUMMARY

Background: Myelodysplastic syndromes (MDS) are malignant stem-cell diseases that are usually diagnosed in elderly patients who present with anemia or, less commonly, bi- or pancytopenia. Their incidence in persons over age 80 is above 50 new cases per 100 000 persons per year. Their clinical course is highly variable. About one-quarter of all patients with MDS develop acute leukemia. The median survival time from the moment of diagnosis is about 30 months.

Methods: We selectively searched the PubMed database for pertinent articles and guidelines from the years 2000–2013. We used the search term “myelodysplastic syndromes.”

Results: MDS are diagnosed by cytology, with consideration of the degree of dysplasia and the percentage of blast cells in the blood and bone marrow, and on a cytogenetic basis, as recommended in the WHO classification. In particular, chromosomal analysis is necessary for prognostication. The Revised International Prognosis Scoring System (IPSS-R) enables more accurate prediction of the course of disease by dividing patients into a number of low- and high-risk groups. The median survival time ranges from a few months to many years. The approved treatments, aside from transfusion therapy, include iron depletion therapy for low-risk patients, lenalidomide for low-risk patients with a deletion on the long arm of chromosome 5, and 5-azacytidine for high-risk patients. High-risk patients up to age 70 who have no major accompanying illnesses should be offered allogenic stem-cell transplantation with curative intent. The cure rates range from 30% to 50%. Mucositis, hemorrhages, infections, and graft-versus-host diseases are the most common complications of this form of treatment.

Conclusion: Myelodysplastic syndromes are treated on an individualized, risk-adapted basis after precise diagnostic evaluation and after assessment of the prognosis. More studies are needed so that stage-adapted treatment can be improved still further.

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The myelodysplastic syndromes (MDS) are among the commonest hematological malignant diseases, with an incidence of around 4 per 100 000 head of population per year and a prevalence of about 7 in 100 000 (1). The incidence of MDS rises sharply with advancing age, reaching over 50 per 100 000/year in the age group over 80 years (e1). Median age at disease onset is around 70 years; only about 10% of patients are below the age of 50 (2). The main symptoms are signs of hematopoietic insufficiency, particularly symptoms of anemia; less often, susceptibility to infection and signs of bleeding occur.

The MDS are diseases of the hematopoietic stem cells. They are characterized by disturbances of differentiation and maturation, and by changes in the bone marrow stroma (3, 4). These are accompanied not only by reduced blood cell counts, but also by an increased risk (about 20% to 25%) of developing acute myeloid leukemia (AML) (4, e2). The disease course varies greatly from patient to patient, with median survival times ranging from a few months to many years (e2). For this reason, particularly with a view to choosing treatment, it is very important to estimate the prognosis as accurately as possible. In recent years a new classification and new prognostic scoring systems have been developed. In addition, new drugs have been shown to be effective and have been introduced into the treatment of MDS patients.

The present review is based on a selective literature search and takes account of the National Comprehensive Cancer Network guidelines (5), the European Leukemia Net guidelines (6), and the guidelines of the German Society of Hematology and Oncology (Deutsche Gesellschaft für Hämatologie und Onkologie) (7).

Diagnosis

In most cases, those involved in diagnosing MDS (*Box*) are family doctors and hematologists. This is because it is often the family doctor who identifies anemia during a routine examination, or else MDS is identified on the basis of blood tests carried out to investigate the cause of symptoms of anemia. Once the more frequent causes of anemia have been ruled out, such as iron deficiency, vitamin B₁₂ and folic acid deficiency, and hemolysis, referral to a hematologist for further investigation is advisable. In particular, the presence of bi- or pancytopenia (about 30%) can be a warning signal (red flag)

TABLE 1

Differential diagnoses in myelodysplastic syndrome and appropriate diagnostic tests for identifying myelodysplastic syndromes

Differential diagnosis	Diagnostic tests
Aplastic anemia, pure red cell aplasia (PRCA)	Histology, cytology, parvovirus B19
Toxic bone marrow injury (alcohol, lead, NSAR, etc.)	History, lab tests
Reactive bone marrow changes (sepsis, HIV, chronic infections, Tbc, autoimmune diseases etc.), copper deficiency	Cytology, history, lab tests
Monocytosis of other etiology	History, lab tests, molecular genetic testing
Paroxysmal nocturnal hemoglobinuria (PNH)	Immunophenotyping
Immune thrombocytopenia	History, course
Megaloblastic anemia	Vitamin B12/folic acid concentration
Hypersplenic syndromes	History/clinical features (splenomegaly)
Acute leukemia (especially erythroleukemia, FAB-M6)	Cytology, genetic and molecular genetic testing
Myeloproliferative diseases (especially aCML, PMF)	Histology, cytogenetic and molecular genetic testing
Hairy cell leukemia, LGL	Cytology, immunophenotyping, molecular genetic testing (braf, stat3), T-cell receptor
Congenital dyserythropoietic anemia (rare)	Molecular genetic (sec23b und cdan-1)

NSAR, nonsteroidal antiinflammatories; Tbc, tuberculosis; aCML, atypical chronic myeloid leukemia; PMF, primary myelofibrosis; LGL, large granular lymphoma

and may indicate bone marrow disease. If blood cell counts and the differential cell count are normal, MDS is extremely unlikely. Patients who have undergone chemotherapy for any other disease, benign or malignant, especially with alkylating drugs (cyclophosphamide, ifosfamide, carmustine, dacarbazine, and others) and/or radiation therapy or radioiodine therapy in the past are at greater risk of developing MDS: around 10% of MDS patients developed the disease after treatment with cytotoxic agents or radiation (8, 9). Occupational history and any notifications to the employers' liability insurance association (10) appear to be important if there is a possibility that there may have been long-term (many years) exposure to benzene, since this increases the risk of MDS. Once hematological and nonhematological differential diagnoses have been ruled out (Table 1), careful cytomorphological analysis of blood and bone marrow are necessary, ideally performed by an experienced hematologist or pathologist. It is not unusual, however, for even experienced diagnosticians to fail to make a definite diagnosis, and for this reason repeat bone marrow investigations can sometimes be necessary if the cytopenia persists.

In many patients, the differential blood tests show signs of dysplasia in the granulocytes. Bone marrow cytology usually shows several signs of dysplasia,

affecting more than 10% of the nucleated cells of one or more cell lineages (e3). None of the signs of dysplasia is pathognomonic of MDS, as the myeloproliferative syndromes, AML, and other hematological and non-hematological diseases can all show dysplasias. *eTable 1* shows the current WHO classification of MDS and the myelodysplastic–myeloproliferative dysplasias (11, 12). Important decision criteria are:

- the extent of the signs of dysplasia (only one cell lineage affected, or several?),
- the degree of blast proliferation (<5%, 5% to 9%, or ≥ 10% to 19%), and
- evidence of a deletion on the long arm of chromosome 5 (del(5q)).

The aim of the classification is to define MDS types with different prognoses. A distinction is made between refractory cytopenia with unilineage dysplasia (RCUD) and refractory anemia with ring sideroblasts (RARS) as entities in which the signs of dysplasia are limited to erythropoiesis, and refractory cytopenia with multilineage dysplasias (RCMD), in which two or, usually, three cell lineages are dysplastic. With a median survival time of about 3 years, patients with RCMD have a poorer prognosis and a higher risk of leukemia than those with RCUD and RARS (median survival about 6 years). If the cytogenetic analysis shows an isolated del(5q) without excess of blasts, a diagnosis of MDS with del(5q) is made. This entity has a good prognosis so long as it does not transform into leukemia (13). In patients with refractory anemia with excess of blasts (RAEB I or II), the presence of a malignant cell population in the bone marrow has been shown, with blasts making up 5% to 9% of cells in RAEB I and 10% to 19% of cells in RAEB II. These patients have a much higher risk of developing AML, and mean survival is about 1 to 2 years (e2). Chronic myelomonocytic leukemia (CMML I and II) and refractory anemia with ring sideroblasts with thrombocytosis (RARS-T) both belong to the group of myelodysplastic–myeloproliferative neoplasias (12–14) and display characteristics of myeloproliferative syndromes, expressed in CMML as a proliferation of monocytes and splenomegaly (e1) and in RARS-T as thrombocytosis and, frequently, evidence of sf3b1 and jak2 mutations (e4, e5). Cases where more than 20% of the cells in bone marrow or blood are blasts are classed as acute leukemia.

Histomorphological analysis of a bone marrow biopsy is a necessary part of the diagnostic work-up in order to determine the presence of bone marrow fibrosis, which is associated with a poorer prognosis (15).

Chromosome analysis of 20 to 25 metaphases (e6) of the bone marrow cells is essential, in particular with a view to estimating the prognosis (16–18). Around 50% to 60% of patients show cytogenetic abnormalities (16). The German–Austrian MDS Working Group together with other international groups has identified the paramount prognostic significance of chromosomal findings and has undertaken a new grouping of different karyotypes (Table 2) (17). In the few cases of dry tap (punctio sicca), in which no bone marrow can be

aspirated, the cytogenetic analysis can be carried out on blood cells. Fluorescence in situ hybridization (FISH) can also be carried out on blood cells, and is particularly successful on CD34+ selected cells. This method can also be employed during the course of the disease for treatment monitoring (e7). In addition, there is the possibility of submitting bone marrow specimens from biopsy in isotonic saline solution and blood for cytogenetic analysis.

Assessment of prognosis

The course of the disease, and hence the prognosis, are essentially determined by disease-specific characteristics such as bone marrow blast cells, chromosomal abnormalities, and the extent of hematopoietic insufficiency, but also by patient-specific factors such as age, sex, comorbidities, and transfusion requirement (19, e8–e12). Prognostic scores combine prognostic factors with the aim of identifying low-risk patients, for whom a wait-and-see approach seems justified, and high-risk patients, who so far as possible should be offered more intensive treatment, including allogeneic blood stem cell transplantation.

The International Prognostic Scoring System (IPSS) is used in both routine clinical practice and in clinical studies (20). Recently, a multinational working group refined the IPSS on the basis of retrospective data from over 7000 patients (IPSS-R) (21). The main innovations are:

- new grouping of chromosomal abnormalities into five rather than three risk categories (17),
- new definition of risk groups depending on the proportion of medullary blast cells (>2%, 3% to 4%, 5% to 9%, 10% to 19%) (e13),
- account taken of the grade of cytopenia.

This prognostic score defines five risk groups (Table 2) that differ significantly in terms of median survival and risk of developing AML. Patients in the very high risk group have a median survival time of only 0.8 years, whereas median survival for patients in the very low risk group is 8.8 years, hardly different from the life expectancy of the age-matched healthy population (21). The score can also be calculated by computer after input of the required parameters (www.mds-foundation.org). The score has not yet been prospectively validated.

Other prognostic factors already established earlier, such as bone marrow fibrosis (15), lactate dehydrogenase (LDH) (e14–e15), β_2 -microglobulin (e16), and transfusion requirement (19) have been confirmed.

For patients with CMML, too, a new score has been developed and validated that uses a medullary blast cell proportion of >10%, leukocyte count of >13 000/ μ L, transfusion requirement, and a poor karyotype as risk factors to define four risk groups (22) (eTable 2). The MDS Comorbidity Score—a validated score for patients with MDS—uses only patient-associated risk factors, namely cardiac, hepatic, renal, and pulmonary comorbidities together with evidence of a solid tumor (23) (eTable 3). Molecular abnormalities are found in

BOX

How to diagnose myelodysplastic syndromes*

● Peripheral blood

- **Blood count, mandatory**
 - Leukocyte count often <4000/ μ L
 - Platelet count often <100 000/ μ L
 - Hemoglobin often <12 g/dL
 - Reticulocyte count often low
- **Differential blood count, manual, mandatory** (dysplasia? percentage of blast cells?)
- **LDH U/L** (above the norm is associated with poorer prognosis)
- **Ferritin**
 - If values >1000 μ g/L, iron chelation therapy may be indicated
- **Erythropoietin concentration**
 - If values <500 U/L, erythropoietin therapy may be indicated (off label)
- **HLA typing in younger patients**
 - Allogeneic transplantation may be indicated

● Bone marrow

- **Cytology** with myeloperoxidase stain, esterase stain, and staining for iron (dysplasia? percentage of blast cells?), mandatory
- **Cytogenetic testing**, may include FISH (chromosomal abnormalities?), mandatory
- **Histological analysis** of a bone marrow sample (cellularity? fibrosis?), mandatory
- **Immunophenotyping**, recommended [6]

● Peripheral blood or bone marrow

- **Mutation analysis**, suggested [6]
 - bcr-abl, pdgfr- α/β , (distinguish between CMML/CML/aCML)
 - tet2, runx1, asxl1, sf3b1, srsf2, tp53, u2af1, dnmt3a, zrsr2, ezh2, nras, kras (if needed to confirm diagnosis, prognosis)

*Source: (5–7). FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; HLA, human leukocyte antigen; CML, chronic myeloid leukemia; aCML, atypical chronic myeloid leukemia

about 71% of patients with MDS and 93% of patients with CMML, and can be used for diagnostic and prognostic purposes in cases where cytogenetic abnormalities are absent and sufficient cytological criteria are lacking (24–26, e17–e25). For five abnormalities (tp53, especially in MDS del(5q), etv6, runx1, asxl1, ezh2), an independent unfavorable prognostic effect was shown. Evidence of an sf3b1 mutation is associated with anemia with ring sideroblasts and evidence of an srsf2 mutation with CMML. Recent investigation techniques such as proteomics or gene array analysis are of great scientific interest but are not yet included among routine clinical diagnostic procedures (e17–e25).

Once a precise diagnosis and estimated prognosis have been made, and unless only mild cytopenia is

TABELLE 2

Definition of the revised International Prognostic Scoring System (IPSS-R) (21)

Score	0	0.5	1	1.5	2	3	4
Cytogenetic risk group	Very good	–	Good	–	Intermediate	Poor	Very poor
Bone marrow blasts	<2%	–	3–4%	–	5–9%	>10%	–
Hemoglobin g/dL	>10	–	8–<10	<8	–	–	–
Platelets/μL	>100	50–<100	<50	–	–	–	–
Granulocytes/μL	>800	<800	–	–	–	–	–

Cytogenetic risk groups

	Cytogenetic abnormalities
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q), single and double, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any other single or double abnormality, independent clones
Poor	–7, inv(3)/t(3q)/del(3q), 2 abnormalities including –7/del(7q), complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

Prognostic risk groups

	Points (IPSS-R)	Median survival time ^{*1}	AML 25% ^{*2}
Very good	<1.5	8.8	Usually not reached
Good	>1.5–3	5.3	10.8
Intermediate	>3–4.5	3	3.2
Poor	>4.5–6	1.6	1.4
Very poor	>6	0.8	0.73

^{*1} In years; AML, acute myeloid leukemia ^{*2} Time until 25% of patients developed leukemia, in years

present that does not require treatment, the patient should be offered appropriate therapy taking into account his or her age, general condition of health, comorbidities (if any), and wishes. Repeat bone marrow diagnostic tests should be carried out if cell counts deteriorate.

Treatment

Recommendations for treatment are based primarily on guidelines by international working groups and only to a small extent on phase III studies. The evidence level is therefore often not very high. A basic principle is that, for low-risk patients, the priority is maintenance or restoration of quality of life, whereas for high-risk patients, prolonging life expectancy is also an important therapeutic goal (7). Treatment should not be delayed until leukemia has developed, but should start as soon as the patient has complaints that impair his or her quality of life or has a high-risk profile. The mainstay of all treatments is transfusion of red blood cell concentrates and, for patients with bleeding and/or platelet counts in single figures, platelet concentrates. The use of red blood cell concentrates should not be guided primarily by hemoglobin values, but should be directed

according to individual need (7). Typically, transfusions are given to patients with hemoglobin values below 8 to 9 g/dL. Supportive therapies include vaccinations in accordance with the recommendations of the German Standing Committee on Vaccination (STIKO, Ständige Impfkommission), early use of antibiotics in cases of fever, and tranexamic acid in patients with marked thrombocytopenia and bleeding diathesis (5–7).

Low-risk patients

Patients with a chronic transfusion requirement develop iron overload, which can lead to organ damage. For this reason, for low-risk patients who have received at least 25 red blood cell concentrates and whose serum ferritin concentration is over 1000 ng/mL, treatment with a chelating agent should be considered. A survival advantage from iron chelation has been shown in retrospective analysis but not yet proven in a prospective randomized trial. Iron chelation therapy leads to improved cell counts in about 15% to 20% of patients (27). Since iron overload is associated with higher complication rates after allogeneic stem cell transplantation, patients should also be treated with an approved

Figure 1

Treatment algorithm for myelodysplastic syndrome in patients with very low, low, or intermediate risk profile (1) (adapted from [5–7]). Dark olive boxes: approved treatment in Europe; red boxes: recommended but not approved; EPO, erythropoietin

chelating agent—deferoxamine or, if deferoxamine is contraindicated, desferasirox—before transplantation (28, e26, e27) (evidence level IIa).

Two-thirds of low-risk patients with an endogenous erythropoietin concentration of <500 U/L and only mild transfusion requirement become transfusion-free with high dose therapy with erythropoietin (29, 30). However, the erythropoietins have not yet been approved for treatment of patients with MDS (evidence level Ib).

Around two-thirds of patients with deletion (5q) without excess of blasts over 9% become transfusion-free after treatment with lenalidomide (31). Lenalidomide is approved for the treatment of transfusion-dependent patients with isolated del(5q) in the IPSS low- and intermediate-risk groups (evidence level IIa). tp53 mutations in patients with MDS and del(5q) are associated with a poorer prognosis (e28).

High-risk patients

Basically, allogeneic blood stem cell transplantation is the only therapeutic measure that offers a potential cure to appropriate patients (e29). This treatment is appropriate for patients aged up to 70 years without relevant comorbidities. In exceptional cases, patients aged over 70 have successfully undergone transplantation (32). The time point for transplantation is largely determined by the disease pathology. In patients with low and intermediate disease risk, transplantation should not be carried out until progression occurs (33). High-risk patients benefit from early transplantation (34). In individual cases, marked cytopenia can be an indication for transplantation (34). Transplants from HLA-matched unrelated donors are today equivalent to those from

HLA-identical sibling donors. Current data even show that, for older patients, younger unrelated donors given better outcomes than “old” sibling donors (35). If transplantation is indicated and a donor has been identified, high-risk patients should undergo transplantation without delay (36).

The intensity of chemotherapy immediately preceding the transplantation (“conditioning”) should be individually adjusted to the patient’s age and comorbidities. Doses are reduced for older patients, while young patients receive high-dose therapy, because both cytotoxic and immunological mechanisms are essential for successful transplantation (37). Post-transplantation aftercare is particularly important, so that complications and any incipient relapse may be recognized at an early stage. The main complications are direct consequences of the conditioning, such as mucositis, bleeding, and infection during the time of cytopenia, and acute and chronic graft-versus-host disease, which can damage organs directly or indirectly, since the immune suppression required to treat it promotes severe bacterial and viral infections. At present, the therapy-related mortality rate is between 15% and 30%. Around 30% to 50% of patients can be cured by allogeneic transplantation, and in 30% to 50% the MDS recurs (38).

Since the hematopoietic cells in MDS patients also show epigenetic changes in the form of pathological DNA hypermethylation, treatment with the demethylating drug 5-azacitidine may be considered. Once this drug was shown in an international phase III study to be superior to other forms of treatment (supportive treatment alone, low-dose AraC, intensive chemotherapy) and to prolong median survival by 10 months (39), it was approved for the treatment of patients with a poor

Treatment algorithm for myelodysplastic syndrome in patients with intermediate (2), high, or very high risk profile, adapted from (5–7).

Dark olive boxes: approved treatment in Europe;
red boxes: participation recommended

FIGURE 2

risk profile (evidence level Ib). The overall response rate is around 50%, but the treatment is not curative (39). The main unwanted effect is deterioration of blood cell counts at the start of treatment, which does not mean that treatment should be stopped (40). Treatment outcome should not be assessed until after six cycles of therapy (40). Induction chemotherapy can be used in high-risk patients with a good karyotype (5–7, e30).

Patients with CMML who develop leukocytosis ($>20\,000/\mu\text{L}$) can also be treated with oral hydroxyurea or low-dose cytarabine (evidence level IIa). *Figures 1 and 2* show the current treatment algorithm for the various risk groups.

In the long-term, patient management requires intelligent multidisciplinary collaboration between the family doctor, the hematologist, and the MDS center involved (if any). Regular (e.g. monthly) cell counts in peripheral blood and assessment of the patient's general state of health can be done by the family doctor. Any transfusions or medical treatment required are carried out by the specialist hematologist, while, especially where approved drugs are unavailable or the patient ceases to respond to treatment, MDS centers can contribute expertise and the opportunity of involvement in clinical studies.

It is in this context that the German MDS Study Group has long been working hard to carry out studies, usually multicenter, in order to offer treatment to as many patients as possible. These are “investigator-

initiated trials” and trials run by the pharmaceutical industry. The MDS Registry in Düsseldorf collects diagnostic, clinical, prognostic, and therapeutic data recorded in many participating centers, in order to enable joint scientific projects. A German Cancer Aid-supported project (Krebshilfeverbundprojekt) (chair: W.K. Hofmann, Mannheim) involves central biobanking in Düsseldorf and research subprojects in Mannheim, Göttingen, Hannover, Regensburg, and Freiburg (www.mds-verbund.de). An up-to-date overview of clinical studies and contacts in the various centers, together with publications of the German–Austrian–Swiss MDS Group may be seen at www.mds-reg-ister.de.

Conflict of interest statement

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Professor Haas declares that no conflict of interest exists.

KEY MESSAGES

- The myelodysplastic syndromes (MDS) are a group of common malignant stem cell diseases, mainly encountered in older people; their clinical course varies greatly and they carry an increased risk of acute leukemia.
- The diagnosis of MDS requires analysis of blood and bone marrow morphology and cytogenetic analysis.
- The prognosis may be estimated using the revised International Prognostic Scoring System (IPSS-R), which defines five risk groups with varying expected survival times and varying risks of leukemia.
- Treatment is adapted to the patient's risk profile and comorbidities, and ranges from transfusion therapy to iron chelation treatment, administration of lenalidomide and 5-azacitidine, or allogeneic transplantation.
- High-risk patients below the age of 70 should be offered curative allogeneic stem cell transplantation, which has a cure rate of 30% to 50%.

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REFERENCES

1. Neukirchen J, Schoonen WM, Strupp C, et al.: Incidence and prevalence of myelodysplastic syndromes: Data from the Düsseldorf MDS-registry. *Leuk Res* 2011; 35: 1591–6.
2. Kuendgen A, Strupp C, Aivado M, et al.: Myelodysplastic syndromes in patients younger than age 50. *J Clin Oncol* 2006; 34: 5358–65.
3. Geyh S, Oz S, Cadeddu RP, et al.: Insufficient stromal support in MDS results from molecular and functional deficits of mesenchymal stromal cells. *Leukemia* 2013; doi: 10.1038/leu.2013.193 (epub ahead of print).
4. Germing U, Gattermann N, Strupp C, et al.: Myelodysplastische Syndrome: Neue WHO-Klassifikation und Aspekte zur Pathogenese, Prognose und Therapie. *Dtsch Arztebl* 2001; 98(36): A-2272–8.
5. National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. Version 2. 2014. 21. 5. 2013.
6. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al.: Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European Leukemia Net. *Blood* 2013; (in press).
7. Hofmann WK, Platzbecker U, Stauder R, Passweg J, Germing U: Leitlinie Myelodysplastische Syndrome, Onkopedia, Deutsche Gesellschaft für Hämatologie und Onkologie, 2013. www.dgho-onkopedia.de/de/onkopedia/leitlinien/mds. Last accessed on 14 October 2013.
8. Bhatia R, Deeg HJ. Treatment-related myelodysplastic syndrome: molecular characteristics and therapy. *Curr Opin Hematol*. 2011; 18: 77–82.
9. Schroeder T, Kuendgen A, Kayser S, et al.: Therapy-related myeloid neoplasms following treatment with radioiodine. *Haematologica* 2012; 97: 206–12.
10. Beelte S, Haas R, Germing U, Jansing PJ: Practice of recognizing benzene-caused occupational diseases in 2006. *Med Klin* 2008; 103: 553–60.
11. Brunning RD, Orazi A, Germing U, et al.: Myelodysplastic syndromes/ neoplasms, overview. In: Swerdlow SH, Campo E, Harris NL, et al.: WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC press 2008.
12. Orazi A, Bennett JM, Germing U, et al.: Chronic Myelomonocytic leukemias. In: Swerdlow SH, Campo E, Harris NL, et al.: WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC press 2008.
13. Germing U, Lauseker M, Hildebrandt B, et al.: Survival, prognostic factors and rates of leukemic transformation in 381 untreated patients with MDS and del(5q): A multicenter study. *Leukemia* 2012; 26: 1286–92.
14. Broseus J, Florensa L, Zipperer E, et al.: Clinical features and course of refractory anemia with ring sideroblasts associated with marked thrombocytosis. *Haematologica* 2012; 97: 1036–41.
15. Buesche G, Teoman H, Wilczak W, et al.: Marrow fibrosis predicts early fatal marrow failure in patients with myelodysplastic syndromes. *Leukemia* 2008; 22: 313–22.
16. Haase D, Germing U, Schanz J, et al.: New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. *Blood* 2007; 110: 4385–95.
17. Schanz J, Tüchler H, Sole F, et al.: New Comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database. *J Clin Oncol* 2012; 30: 820–9.
18. Schanz J, Tüchler H, Solé F, et al.: Monosomal karyotype in MDS: explaining the poor prognosis? *Leukemia* 2013; doi: 10.1038/leu.2013.187 (epub ahead of print).
19. Malcovati L, Germing U, Kuendgen A, et al.: Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol* 2007; 25: 3503–10.
20. Greenberg P, Cox C, LeBeau MM, et al.: International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997; 89: 2079–88.
21. Greenberg PL, Tuechler H, Schanz J, et al.: Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–65.
22. Such E, Germing U, Malcovati L, et al.: Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. *Blood* 2013; 121: 3005–15.
23. Della Porta MG, Malcovati L, Strupp C, et al.: Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica* 2011; 96: 441–9.
24. Bejar R, Stevenson KE, Caughey BA, et al.: Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol* 2012; 30: 3376–82.
25. Bejar R, Stevenson K, Abdel-Wahab O, et al.: Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med* 2011; 364: 2496–50.
26. Graubert T, Walter MJ: Genetics of myelodysplastic syndromes: new insights. *Hematology Am Soc Hematol Educ Program* 2011; 2011: 543–9.
27. Gattermann N, Finelli C, Della Porta M, et al.: Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes. *Haematologica* 2012; 97: 1364–71.
28. Gattermann N: Overview of guidelines on iron chelation therapy in patients with myelodysplastic syndromes and transfusional iron overload. *Int J Hematol* 2008; 88: 24–9.
29. Greenberg PL, Sun Z, Miller KB, et al.: Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). *Blood* 2009; 114: 2393–400.

30. Hellström-Lindberg E, Gulbrandsen N, Lindberg G, et al.: A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *Br J Haematol* 2003; 12: 1037–46.
31. List A, Dewald G, Bennett J, et al.: Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 2006; 355: 1456–65.
32. de Witte T, Hagemeijer A, Suci S, et al.: Value of allogeneic versus autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. final results of a prospective randomized european intergroup trial. *Haematologica* 2010; 95: 1754–61.
33. McClune BL, Weisdorf DJ, Pedersen TL, et al.: Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol* 2010; 28: 1878–87.
34. Cutler CS, Lee SJ, Greenberg P, et al.: A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood* 2004; 104: 579–85.
35. Kroger N, Zabelina T, de Wreede, et al.: Allogeneic stem cell transplantation for older advanced MDS patients: improved survival with young unrelated donor in comparison with HLA-identical siblings. *Leukemia* 2013; 27: 604–9.
36. Saure C, Schroeder T, Zohren F, et al.: Upfront allogeneic blood stem cell transplantation for patients with high-risk myelodysplastic syndrome or secondary acute myeloid leukemia using a FLAMSA-based high-dose sequential conditioning regimen. *Biol Blood Marrow Transplant* 2012; 18: 466–72.
37. Luger SM, Ringden O, Zhang MJ, et al.: Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. *Bone Marrow Transplant* 2012; 47: 203–11.
38. Mufti GJ, Potter V: Myelodysplastic syndromes: who and when in the course of disease to transplant. *Hematology Am Soc Hematol Educ Program* 2012; 2012: 49–55.
39. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al.: Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; 10: 223–32.
40. Götze K, Platzbecker U, Giagounidis A, et al.: Azacitidine for treatment of patients with myelodysplastic syndromes (MDS): practical recommendations of the German MDS Study Group. *Ann Hematol* 2010; 89: 841–50.

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REVIEW ARTICLE

Myelodysplastic Syndromes: Diagnosis, Prognosis, and Treatment

Ulrich Germing, Guido Kobbe, Rainer Haas, Norbert Gattermann

eREFERENCES

- e1. Williamson PJ, Kruger AR, Reynolds PJ, Hamblin TJ, Oscier DG: Establishing the incidence of myelodysplastic syndrome. *Br J Haematol* 1994; 87: 743–5.
- e2. Germing U, Aul C, Niemeyer CM, Haas R, Bennett JM: Epidemiology, classification and prognosis of adults and children with myelodysplastic syndromes. *Ann Hematol* 2008; 87: 691–9.
- e3. Germing U, Strupp C, Giagounidis A, et al.: Evaluation of dysplasia through detailed cytomorphology in 3156 patients from the Düsseldorf Registry on myelodysplastic syndromes. *Leuk Res* 2013; 36: 727–34.
- e4. Broséus J, Alpermann T, Wulfert M, et al.: Age, JAK2V617F and SF3B1 mutations are the main predicting factors for survival in refractory anaemia with ring sideroblasts and marked thrombocytosis. *Leukemia* 2013; doi: 10.1038/leu.2013.120 (epub ahead of print).
- e5. Yoshida K, Sanada M, Shiraishi Y, et al.: Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature* 2011; 478: 64–9.
- e6. Steidl C, Steffens R, Gassmann W, et al.: Adequate cytogenetic examination in myelodysplastic syndromes: analysis of 529 patients. *Leuk Res* 2005; 29: 987–93.
- e7. Braulke F, Schanz J, Jung K, et al.: FISH analysis of circulating CD34+ cells as a new tool for genetic monitoring in MDS: verification of the method and application to 27 MDS patients. *Leuk Res* 2010; 34: 1296–301.
- e8. Sperr WR, Wimazal F, Kundi M, et al.: Comorbidity as prognostic variable in MDS: comparative evaluation of the HCT-CI and CCI in a core dataset of 419 patients of the Austrian MDS Study Group. *Ann Oncol* 2010; 21: 114–9.
- e9. Zipperer E, Pelz D, Nachtkamp K, et al.: The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome. *Haematologica* 2009; 94: 729–32.
- e10. Valent P, Hofmann WK, Büsche G, et al.: Meeting report: Vienna 2008 Workshop of the German-Austrian working group for studying prognostic factors in myelodysplastic syndromes. *Ann Hematol* 2009; 88: 607–11.
- e11. Nösslinger T, Tüchler H, Germing U, et al.: Prognostic impact of age and gender in 897 untreated patients with primary myelodysplastic syndromes. *Ann Oncol* 2010; 21: 120–5.
- e12. Valent P, Horny HP, Bennett JM, et al.: Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference. *Leuk Res* 2007; 31: 727–36.
- e13. Germing U, Kündgen A: Prognostic scoring systems in MDS. *Leuk Res* 2012; 36: 1463–9.
- e14. Germing U, Hildebrandt B, Pfeilstöcker M, et al.: Refinement of the international prognostic scoring system (IPSS) by including LDH as an additional prognostic variable to improve risk assessment in patients with primary myelodysplastic syndromes (MDS). *Leukemia* 2005; 19: 2223–31.
- e15. Aul C, Gattermann N, Heyll A, et al.: Primary myelodysplastic syndromes: analysis of prognostic factors in 235 patients and proposals for an improved scoring system. *Leukemia* 1992; 6: 52–9.
- e16. Neumann F, Gattermann N, Barthelmes HU, et al.: Levels of beta 2 microglobulin have a prognostic relevance for patients with myelodysplastic syndrome with regard to survival and the risk of transformation into acute myelogenous leukemia. *Leuk Res* 2009; 33: 232–6.
- e17. Meggendorfer M, Roller A, Haferlach T, et al.: SRSF2 mutations in 275 cases with chronic myelomonocytic leukemia (CMML). *Blood* 2012; 120: 3080–8.
- e18. Thol F, Friesen I, Damm F, et al.: Prognostic significance of ASXL1 mutations in patients with myelodysplastic syndromes. *J Clin Oncol* 2011; 29: 2499–506.
- e19. Thol F, Kade S, Schlarmann C, et al.: Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. *Blood* 2012; 119: 3578–84.
- e20. Patnaik MM, Lasho TL, Hodnefield JM, et al.: SF3B1 mutations are prevalent in myelodysplastic syndromes with ring sideroblasts but do not hold independent prognostic value. *Blood* 2012; 119: 569–72.
- e21. Aivado M, Spentzos D, Germing U, et al.: Serum proteome profiling detects myelodysplastic syndromes and identifies CXCL chemokine ligands 4 and 7 as markers for advanced disease. *Proc Natl Acad Sci USA* 2007; 104: 1307–12.
- e22. Hofmann WK, de Vos S, Komor M, et al.: Characterization of gene expression of CD34+ cells from normal and myelodysplastic bone marrow. *Blood* 2002; 100: 3553–60.
- e23. Nowak D, Nolte F, Mossner M, et al.: Genome-wide DNA-mapping of CD34+ cells from patients with myelodysplastic syndrome using 500K SNP arrays identifies significant regions of deletion and uniparental disomy. *Exp Hematol* 2009; 37: 215–24.
- e24. Frobel J, Cadeddu RP, Hartwig S, et al.: Platelet proteome analysis reveals integrin-dependent aggregation defects in patients with myelodysplastic syndromes. *Mol Cell Proteomics* 2013; 12: 1272–8.
- e25. Schildgen V, Wulfert M, Gattermann N: Impaired mitochondrial gene transcription in myelodysplastic syndromes and acute myeloid leukemia with myelodysplasia-related changes. *Exp Hematol* 2011; 39: 666–75.
- e26. Gattermann N, Finelli C, Porta MD, et al.: Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: results from the large 1-year EPIC study. *Leuk Res* 2010; 34: 1143–50.
- e27. Valent P, Krieger O, Stauder R, et al.: Iron overload in myelodysplastic syndromes (MDS)—diagnosis, management, and response criteria: a proposal of the Austrian MDS platform. *Eur J Clin Invest* 2008; 38: 143–9.
- e28. Jädersten M, Saft L, Smith A, et al.: TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. *J Clin Oncol* 2011; 29: 1971–9.
- e29. Platzbecker U, Schetelig J, Finke J, et al.: Allogeneic hematopoietic cell transplantation in patients age 60–70 years with de novo high-risk myelodysplastic syndrome or secondary acute myelogenous leukemia: comparison with patients lacking donors who received azacitidine. *Biol Blood Marrow Transplant* 2012; 18: 1415–21.
- e30. Knipp S, Hildebrandt B, Kündgen A, et al.: Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. *Cancer* 2007; 110: 345–52.

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eTABLE 1

WHO classification of myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasias (11, 12)

MDS subtype	Blood	Bone marrow
Refractory cytopenia with unilineage dysplasia (RCUD) Refractory anemia (RA) Refractory neutropenia (RN) Refractory thrombocytopenia (RT)	<1% blasts Uni- or bicytopenia	<5% blasts Dysplasia in ≥ 10% of cells of only one lineage
Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	<5% blasts, ≥ 15% ring sideroblasts within erythropoiesis, exclusively dyserythropoiesis
Refractory cytopenia with multilineage dysplasia (RCMD) with or without ring sideroblasts	<1% blasts Cytopenia <1000/μL monocytes	<5% blasts, signs of dysplasia in ≥ 10% of cells of 2 to 3 lineages
MDS with isolated del(5q)	<1% blasts Anemia, platelets often increased	Mostly typical mononuclear megakaryocytes, <5% blasts, isolated del(5q) abnormality
Refractory anemia with excess of blasts I (RAEB I)	Cytopenia <5% blasts <1000/μL monocytes	Uni- or multilineage dysplasia, blasts 5% to 9%, no Auer rods
Refractory anemia with excess of blasts II (RAEB II)	Cytopenia <20% blasts <1000/μL monocytes Auer rods may be found	Uni- or multilineage dysplasia, blasts 10% to 19%, Auer rods may be found
Unclassified MDS (MDS-U) RCUD with pancytopenia RCMD/RCUD with 1% blasts in blood MDS-typical chromosomal aberration without clear signs of dysplasia	<1% blasts <1000/μL monocytes	<5% blasts
Myelodysplastic/myeloproliferative neoplasias		
Chronic myelomonocytic leukemia I (CMML I)	<5% blasts Uni- or bicytopenia >1000/μL monocytes No Auer rods	<10% blasts, dysplasia in >10% of cells of 1 to 3 lineages, no Auer rods
Chronic myelomonocytic leukemia II (CMML II)	<20% blasts Uni- oder bicytopenia >1000/μL monocytes Auer rods may be found	<20% blasts, dysplasia in >10% of cells of 1 to 3 lineages, Auer rods may be found
Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T)	Cytopenia >450 000/μL platelets <1% blasts	<5% blasts, >15% ring sideroblasts within erythropoiesis, dysplasia in >10% of cells of 1 to 3 lineages, no Auer rods, often sf3b1 and jak-2 mutations

WHO, World Health Organization; MDS, myelodysplastic syndromes

eTABLE 2

Definition of Chronic Myelomonocytic Leukemia Score (CPSS) (22)

Parameter	Points	2	1	0
WHO type			CMML II	CMML I
Leukocyte count			>13 000/μL	<13 000/μL
Transfusion requirement			Regular	None
Karyotype		Poor	Intermediate	Low
Karyotype groups				
Poor	+8, abnormal chromosome 7, >2 abnormalities			
Intermediate	All other abnormalities			
Risk groups				
Low	0			
Intermediate I	1			
Intermediate II	2–3			
High	4–5			

WHO, World Health Organization; CMML, chronic myelomonocytic leukemia

eTABLE 3

Definition of MDS Comorbidity Score (MDS-CI Score) (23)

Comorbidity	Points
Cardiac disease	2
Moderate to severe hepatic disease	1
Severe pulmonary disease	1
Renal disease	1
Solid tumor	1
Risk groups	
Low risk	0
Intermediate risk	1–2
High risk	>2

MDS, myelodysplastic syndromes