

Myelodysplastic Syndromes

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

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1 Definition and Basic Information

Myelodysplastic syndromes (MDS) are diseases affecting the hematopoietic stem cell. They are characterized by dysplasias of blood and bone marrow cells as well as by hematopoietic deficiency and an increased risk of developing acute myeloid leukemia.

With an incidence rate of approx. 4-5/100,000 inhabitants per year, MDS belong to the most frequently occurring malignant hematological diseases [1]. The incidence rate increases to >30/100,000 after the age of 70 years. The median age at diagnosis is about 75 years. Women are somewhat less often afflicted than men. Therapy-associated MDS (approx. 10%) might appear subsequent to chemotherapy and/or radiotherapy, however, a causative agent cannot be unequivocally identified in approx. 90% of all cases. The cardinal symptom mostly consists of anemia, but also bicytopenia or pancytopenia. The bone marrow is often normocellular, or even hypercellular, or hypocellular in 10% of the cases. Significant to diagnostics are signs of dysplasia which relate to either one or several cell lines. At least 10% of the cells belonging to one cell line must display unequivocal signs of dysplasia in order to diagnose MDS. More than 50% of the patients had chromosomal aberrations at the time of diagnosis [2].

2 Clinical Presentation

Depending on the peripheral cell counts, the symptoms of anemia predominate, less often infections and hemorrhages. Organomegaly and lymphomas are seldom. Over one-half of the patients require transfusions at the time their disease is diagnosed.

3 Diagnostics and Differential Diagnoses

MDS are diagnosed by exclusion, because numerous signs of dysplasia might also occur in the context of other, including non-hematological diseases. It is therefore important to exclude other hematological and non-hematological diseases by applying adequate methods (Table 1). MDS diagnostics comprise differential blood cell counts and an analysis of the bone marrow (Table 2). Of central importance is the cytomorphological characterization including an iron stain, ideally peroxidase, PAS and esterase stains as well, in order to detect the signs of dysplasia and quantify the proportion of monocytic cells and ringed sideroblasts. The cytomorphological determination of the peripheral and medullary proportion of blasts should also proceed as exactly as possible. It is also mandatory to determine whether either 2 or 3 cell lines show signs of dysplasia. Based on these parameters the disease can be assigned to one of the WHO classification types (Table 3 and Table 4) [3, 4].

The current WHO classification on myeloid neoplasms allocates the types of hematological disorders traditionally assigned to MDS to two major groups: Apart from the pure MDS, a group is defined that contains myelodysplastic-myeloproliferative neoplasms. The proportion of blasts

to be found in blood and the bone marrow, which discriminates the disease from an acute leukemia, is defined at 20%. Chromosomal analysis is obligatory for diagnostic, prognostic and therapeutic reasons. Conducive is also the histological analysis of a bone marrow biopsy, particularly in order to assess cellularity and the potential existence of fibrosis.

Immunophenotyping used as a tool to estimate the percentage of blasts and display the signs of dysplasia is gaining more and more importance. However, the accuracy of the method in routine diagnostics must not be overestimated. Molecular biological analyses which demonstrate the existence of PDGFR-alpha/beta and bcr-abl are required to distinguish a CMML from the various forms of myeloproliferative syndromes. In addition, the detection of JAK-2 mutations is essential to classification. Measurement of LDH, ferritin, and the endogenous erythropoietin level round up the basic diagnostics.

Table 1: Differential Diagnoses of MDS

| Differential Diagnosis | Diagnostic Method |
|---|--|
| Aplastic anemia, pure red-cell aplasia (PRCA) | Histology, cytology |
| Toxic bone marrow damage (alcohol, lead, NSAR, etc.) | Medical case history |
| Reactive bone marrow alterations (sepsis, HIV, chronic infections, Tb, autoimmune diseases, etc.) | Cytology, medical case history, laboratory analyses |
| Monocytosis of other etiology | Medical case history, laboratory analyses |
| Paroxysmal nocturnal hemoglobinuria (PNH) | Immunophenotyping |
| Immune thrombocytopenia | Cytology, medical case history, course |
| Megaloblastic anemias | Vitamin B ₁₂ -/folic acid level |
| Hypersplenism | Medical case history/clinical examination/splenomegaly |
| Acute leukemias (especially erythroleukemia, FAB-M6) | Cytology |
| Myeloproliferative diseases (particularly aCML, OMF) | Histology, cytogenetics, molecular biology |
| Hairy-cell leukemia, LGL | Cytology, immunophenotyping |
| Congenital dyserythropoietic anemias (rare) | molecular biology |

Table 2: Diagnostics

| Peripheral Blood | Bone Marrow |
|-------------------------------|---|
| Blood cell count | Cytology incl. Fe, POX, PAS, esterase |
| Reticulocytes | Cytogenetics, if possible, incl. FISH (chromosomes 5, 7, 8) |
| Differential blood cell count | Histology |
| LDH | Immunophenotyping, if possible |
| Ferritin | JAK-2, bcr-abl, PDGFR-alpha/beta |
| Erythropoietin | |
| Folic Acid | |
| Vitamin B12 | |
| HLA typing, if applicable | |

Table 3: WHO Classification of Myelodysplastic Syndromes

| MDS Subtype | Blood | Bone Marrow |
|---|---|---|
| Refractory cytopenia with unilineage dysplasia (RCUD) RA refractory anemia RN refractory. Neutropenia RT refractory thrombocytopenia | <1% blasts unicytopenia or bicytopenia | <5% blasts, dysplasias in $\geq 10\%$ of cells belonging to one cell line |
| Refractory anemia with ringed sideroblasts (RARS) | anemia, no blasts | <5% blasts, $\geq 15\%$ ringed sideroblasts within erythropoiesis, exclusive of dyserythropoiesis |
| Refractory cytopenia with multilineage dysplasias (RCMD), with or without ringed sideroblasts | <1% blasts cytopenia(s) monocytes <1000/ μ l | <5% blasts, signs of dysplasia $\geq 10\%$ of cells belonging to 2-3 cell lines |
| MDS with isolated del(5q) | $\leq 1\%$ blasts anemia, platelets often increased | Mostly typical mononuclear megakaryocytes <5% blasts, isolated del(5q) anomaly |
| Refractory anemia with excess blasts RAEB I | cytopenia(s), <5% blasts, monocytes <1000/ μ l | Unilineage or multilineage dysplasias, blasts 5-9%, no Auer bodies |
| Refractory anemia with excess blasts II RAEB II | cytopenia(s), <20% blasts, monocytes <1000/ μ l | Unilineage or multilineage dysplasias, blasts 10-19%, Auer bodies possible |
| Unclassified MDS 1. RCUD with pancytopenia 2. RCMD/RCUD with 1% blasts in the blood 3. MDS-typical chromosomal aberration without clear signs of dysplasia | $\leq 1\%$ blasts, monocytes <1000/ μ l | <5% blasts |

Table 4: WHO Classification of Myelodysplastic/Myeloproliferative Neoplasms

| Type | Blood | Bone Marrow |
|--|--|---|
| Chronic myelomonocytic leukemia I (CMML I) | <5% blasts unicytopenia or bicytopenia monocytes >1000/ μ l no Auer bodies | <10% blasts, dysplasias in >10% of cells belonging to 1-3 cell lines, no Auer bodies |
| Chronic myelomonocytic leukemia II (CMML II) | <20% blasts unicytopenia or bicytopenia monocytes >1000/ μ l Auer bodies possible | <20% blasts, dysplasias in >10% of cells belonging to 1-3 cell lines, Auer bodies possible |
| Refractory anemia with ringed sideroblasts and thrombocytosis (RARS-T) | cytopenia(s), platelets >450,000/ μ l $\leq 1\%$ blasts | <5% blasts, >15% ringed sideroblasts within erythropoiesis, dysplasias in >10% of cells belonging to 1-3 cell lines, no Auer bodies, frequent JAK-2 mutations |

4 Prognosis

Apart from age, sex, and comorbidities especially biological disease parameters can be used to estimate the prognosis of the disease. The most important prognostic parameters consist in the percentage of medullary blasts and cytological findings, followed by the transfusion requirement, cell counts, and LDH activity [4]. Two validated prognostic systems which can be applied to assess the individual risk of patients are available (IPSS, WPSS, Table 5 and Table 6) [5- 7]; to this end, a cytogenetic bone marrow analysis will be required. Based on the prognostic score the patients are then allocated to the various risk groups, a procedure which has an essential influence on therapy planning when age, general health condition, and the patient's preferences are taken into account. At present, the impact of chromosomal alterations (weighted relatively low in IPSS) relative to the number of bone marrow blasts (weighted relatively high in IPSS) is being redefined on the basis of large datasets derived from international networks [8].

Table 5: Definition des IPSS (International Prognostic Scoring System)

| Score Value | | | | | |
|-------------------------------|------|--------------|----------------------|-------|-------|
| | 0 | 0,5 | 1 | 1,5 | 2 |
| Blasts (%) | < 5 | 05-10 | - | 11-20 | 21-30 |
| Karyotype* | good | intermediate | bad | | |
| Number of cytopenias** | 0/1 | 2/3 | | | |
| Risk Score | | | Scored Points | | |
| Low risk | | | 0 | | |
| Intermediate risk I | | | 1 | | |
| Intermediate risk II | | | 2 | | |
| High risk | | | 3-4 | | |
| Very high risk | | | 5-6 | | |

Legend:

* good: normal, -Y, del(5q), del(20q). bad: complex (≥ 3 anomalies) or aberrations on chromosome 7. intermediate: other.

** Hemoglobin <100 g/l, Neutrophils <1.8 x 10⁹/l, Platelets <100 x 10⁹/l

Table 6: Definition of the WHO adapted Prognostic Scoring System (WPSS)

| Score Value | | | | |
|-----------------------------|-------------------|----------------------|--------|---------|
| | 0 | 1 | 2 | 3 |
| WHO Type | RCUD / RARS / 5q- | RCMD | RAEB I | RAEB II |
| Karyotype* | good | intermediate | bad | |
| Transfusions** | no | yes | | |
| Risk Score | | Scored Points | | |
| Low risk | | 0 | | |
| Intermediate risk I | | 1 | | |
| Intermediate risk II | | 2 | | |
| High risk | | 3-4 | | |
| Very high risk | | 5-6 | | |

Legend:

* good: normal, -Y, del(5q), del(20q). bad: complex (≥ 3 anomalies) or aberrations on chromosome 7. intermediate: other.

** at least 1 erythrocyte concentrate every 8 weeks over 4months

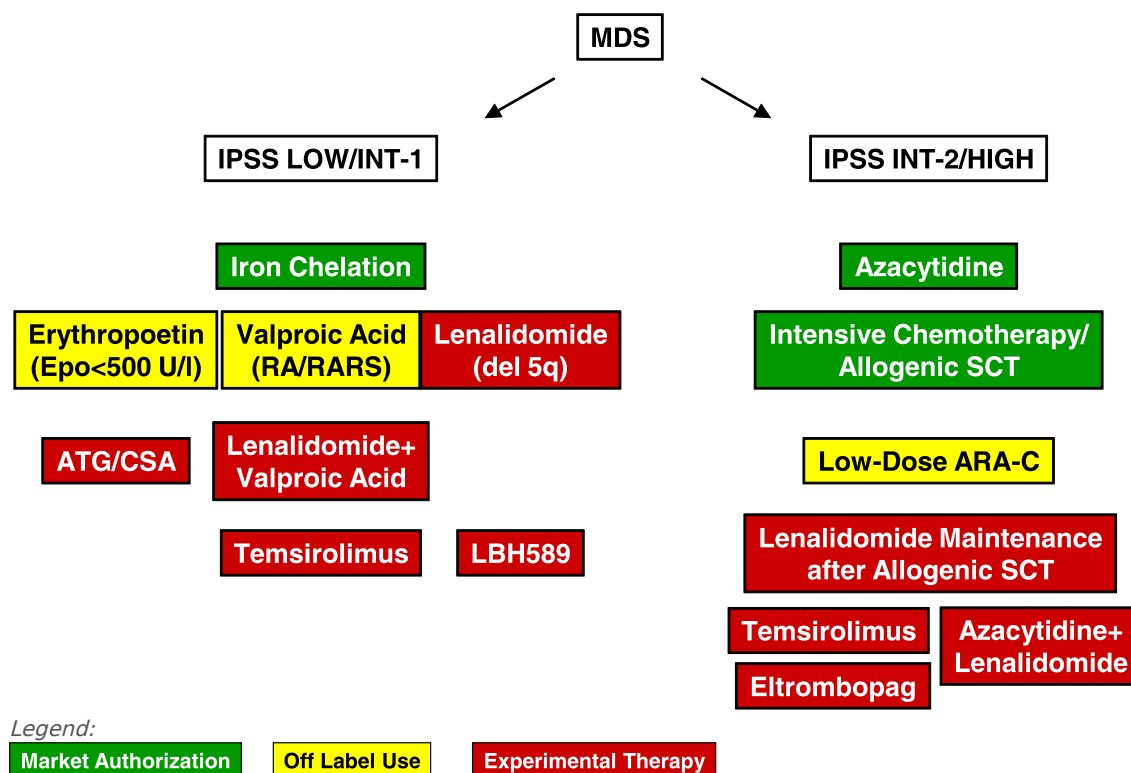
5 Therapy of Low-Risk MDS (IPSS LOW and IPSS INT-1)

5.1 Therapy Indication

A "watch and wait" strategy is fully justified for this small group of MDS patients because cytopenia is of lesser degree. However, anemia is the most frequent indication for the onset of therapy in a considerable number of patients. Anemia results in fatigue especially in elderly patients, an increased incidence of falling with the risk of bone fractures, cognitive deficiencies, lower quality of life, and a shortened overall survival. If a MDS patient requires therapy, the

basics of any therapy will consist of a good supportive therapy which includes transfusions, the administration of antibiotics as needed, as well as an effective treatment of any secondary diseases. The indication for disease-specific therapy depends on the stage of the disease, the patient's age and clinical condition. For the majority of patients, maintenance and/or improvement of the quality of life and personal autonomy in case of elderly patients stand in the center of therapeutic efforts. Figure 1 shows a stage-dependent algorithm of the therapeutic options.

Figure 1: Therapy Options in Myelodysplastic Syndrome



5.2 Supportive Therapy

The main component of supportive therapy consists in the transfusion of erythrocyte concentrates, depending on the patient's clinical condition (not depending on the Hb value; exception: the Hb value should be stabilized above 10g/dl in patients who have severe coronary heart disease and/or other serious secondary diseases). Clinically significant hemorrhages are to be expected especially below the threshold limit of < 10 Gpt/l platelets. However, a substitution of platelet concentrates should not, if possible, be performed prophylactically (exception: fever, serious infection) but only in case of clinical signs of hemorrhages (risk of alloimmunization). Without exception, the therapy decision must be individually adjusted to circumstances of the patient and the healthcare facility (medical office, specialized outpatient department with emergency unit etc.).

The application of antibiotics in case of infections (also including minor infections) should proceed generously, particularly in the case of neutropenic patients. Regular prophylaxis with antibiotics is not recommended (as yet there are no unequivocal data that prove a benefit concerning the number and severity of infections among MDS patients).

The optimal treatment of secondary diseases (lung diseases, heart diseases, etc.) is considered an important part of the entire therapy.

5.3 Iron Chelators

On the long term, polytransfused patients are threatened by accompanying secondary hemochromatosis (hepatopathy, cardiomyopathy). For this reason therapy with iron chelators may be considered in IPSS and WPSS low-risk patients who have a life expectancy of more than two years, received at least 20 erythrocyte concentrates and/or have a ferritin level of >1000 ng/ml (evidence strength Ib, recommendation level A) [9- 11]. Prospective randomized trials on the efficacy and the impact on long-term survival in patients with MDS are currently in progress, however, results are expected in five years at the earliest because of the long follow-up period.

5.4 Hematopoietic Growth Factors

As to the granulocyte colony-stimulating factor (G-CSF), there are no data from fully published prospective randomized clinical trials that justify the application in patients with MDS, exceptions see below. Therapy with G-CSF merely results in a transient rise in the number of neutrophilic granulocytes. Only the recurrent complicated infection associated with severe neutropenia is accepted as an exceptional indication (evidence strength III, recommendation level C).

Therapy with erythropoiesis-stimulating agents (ESAs, classically: erythropoietin 150–300 U/kg b.w. SC 3-times/week or 500 U/kg SC weekly; retarded erythropoietin: 150µg or 300µg SC weekly) results in transfusion independence in 20–25 % of the patients treated. The combination with low doses of G-CSF (100µg G-CSF SC 2-3-times per week, with the intention of modulating the efficacy of erythropoietin, not to increase the leukocyte count - see above) improves the effects of erythropoietin particularly in patients with RARS and otherwise refractory to uncombined erythropoietin therapy.

A response in up to 75% of patients can be expected by considering the predictive factors

- erythropoietin level <200 (500) IU/ml,
- low transfusion dependence (maximum of 2 RBC concentrates in 8 weeks), and
- IPSS low-risk/INT-1 MDS

and selecting patients accordingly (evidence strength Ib, recommendation level A) [12].

The thrombopoietic growth factors (romiplostim, eltrombopag) now available give us the opportunity to successfully treat (the rarely clinically relevant) severe thrombocytopenia in low-risk MDS patients. First results obtained in phase—II studies indicated that a significant improvement of thrombopoiesis can be achieved in about 50% of the patients with platelet values below 50,000 /µl, associated with a lesser incidence of hemorrhagic events (evidence strength IIa, recommendation level B).

5.5 Histone Deacetylase Inhibitors (HDAC Inhibitors)

Valproic acid results in a response of erythropoiesis in up to 50% of MDS patients treated. Therapy with valproic acid is given with escalating doses, starting with 500mg/d. Regular blood-level checks with target levels of 50-100 µg/l are necessary for dose finding. Therapy with valproic acid presents a potential option in patients with low-risk MDS, which does not qualify for therapy with growth factors or immunomodulatory agents [13]. The effectivity of other HDAC inhibitors, e.g. LBH589, is currently under investigation in clinical studies.

5.6 Immunomodulatory Substances

The further development of thalidomide has led to the creation of so-called immunomodulatory derivatives (IMiDs). Their mode of action is not fully understood, however, apart from an inhibition of TNF-alpha it also encompasses an activation of T and NK cells as well as immediate proapoptotic mechanisms.

Therapy with lenalidomide leads to a response in about 60-70% of MDS patients with a single deletion on chromosome 5 (including 5q- syndrome), a condition of transfusion-dependent anemia, and a medullary blast percentage of <5%. The result is a complete transfusion independence and an cytogenetic remission (evidence strength Ib, recommendation level A) [14].

The minimally effective dose has not yet been defined. Standard treatment consists of 10mg/day with dose adjustment depending on the platelet count. Lenalidomide also displays activity in MDS patients who do not have alterations on chromosome 5. The response rates in these cases range from 25-40 % (evidence strength IIa, recommendation level B) [15].

Inhibition of the mTOR signal transduction pathway is a further option of exerting an influence on the disturbed proliferation and differentiation behavior of hematopoiesis in cases of MDS. Clinical trials, e.g. with temsirolimus, are currently conducted with regard to all risk forms of MDS.

5.7 Immunosuppressive Therapy

Therapy with immunosuppressive drugs (similar to the therapy of severe aplastic anemia) depends on the positive experiences made with a subgroup of patients which can be characterized as follows:

- hypocellular bone marrow,
- early form of MDS (IPSS LOW and INT-1), and
- minor transfusion dependence.

About 30% of these patients reach a condition in which they no longer depend on transfusions, whereby particularly patients who are HLA-DR15-positive benefit from this treatment. Immunosuppressive therapy in cases of MDS should exclusively proceed at a hematology healthcare center and in the scope of controlled clinical trials, because of the potential risk of severe adverse effects [16].

The optimal selection of patients for immunosuppressive therapy with alemtuzumab results in a response rate of about 80% in low-risk MDS. However, this therapy has a high risk of serious adverse effects and should also be applied only at a hematological healthcare center and in the scope of controlled clinical trials (evidence strength IIa, recommendation level B) [17].

6 Therapy of High-Risk-MDS (IPSS INT-2 and IPSS HIGH)

6.1 Therapy Indication

When untreated, patients with high-risk MDS (IPSS INT-2 and HIGH) have an unfavorable prognosis which includes a high risk of transformation into a secondary acute leukemia and a median overall survival of only 12 months [5, 7]. Apart from supportive therapy, further treatment options should be considered for each individual patient, depending on the risks of the disease and the existence of accompanying diseases.

6.2 Intensive Chemotherapy

Intensive chemotherapy in analogy to AML treatment is not an established therapy option for high risk MDS patients outside of clinical trials. Whether intensive chemotherapy is a reasonable option in the individual case (e.g. to induce remission prior to scheduled allogeneic stem cell transplantation), can only be decided on the basis of the individual risk-benefit assessment.

6.3 Epigenetic Therapy

Both 5-azacytidine and 5-aza-deoxycytidine are pyrimidine analogues which are incorporated into the DNA instead of cytosine. Both substances have an immediate cytotoxic effect on proliferating cells. In addition, they prevent the methylation of CPG segments (so-called CPG islands) in the DNA by binding irreversibly to DNA methyltransferase (DNMT) and thus causing an inhibition of the enzyme.

The substances mentioned have been tested in several phase-II studies and randomized phase-III studies. Two independent randomized studies revealed an advantage in MDS patients treated with 5-azacytidine compared to those who had received supportive therapy alone [18, 19]. Both studies expressed this benefit in terms of an absolute difference in overall survival of 6-9 months. The difference was statistically significant in the second study (AZA-001) which had included the higher number of patients. In this study, therapy with 5-azacytidine was superior to a standard therapy consisting of supportive treatment alone, or low-dosed Ara-C (LDAC), or intensive anthracycline-based chemotherapy, with respect to median survival, transfusion independence, and improvement of peripheral blood parameters. The AZA-001 study is hence the first randomized study which demonstrated that a therapeutic drug is capable of producing an advantage in the survival of high-risk MDS patients. In contrast, the current randomized EORTC phase-III study failed to prove that a survival advantage for patients with high-risk MDS had resulted from therapy with 5-aza-deoxycytidine. Neither could another randomized study in the United States evidence a statistically significant survival advantage for patients who had been treated with this substance, despite the fact that the response rates and progression-free survival under therapy were also significantly better than under the best supportive treatment [20].

Patients with

- IPSS INT-2/HIGH
- CMML with < 13,000 / μ l leukocytes (dysplastic variant) and
- AML according to WHO with multilinear dysplasia and up to 30% blasts in the bone marrow

can be treated with 5-azacytidine if they do not qualify for allogeneic stem cell transplantation (evidence strength Ib, recommendation level A). The standard AZA-7 regime is administered subcutaneously or intravenously in a dose of 75mg/m² over seven days. The cycles are repeated in intervals of 28 days. As the effect of epigenetic modulation only sets in gradually, at least six cycles of 5-azacytidine should be administered before a response can be assessed. Therapy should be continued if there is a positive response (which should at least consist of an improvement of peripheral blood parameters). The optimum number of cycles has not yet been defined, as very late remissions have been described. It must be assumed that patients who respond will also benefit from the continuous therapy. The application of specific prognostic factors makes it possible to select patients for 5-azacytidine therapy who will most likely respond to therapy and experience a successful extension of overall survival [21]. Therapy should be continued as long as long as the patient responds (evidence strength IV, recommen-

dation level D). Current studies are examining the value of combining demethylating agents with histone deacetylase inhibitors (HDAC inhibitors), or lenalidomide.

6.4 Non-Intensive Chemotherapy

Non-intensive chemotherapy such as low-dose cytarabine (2 x 10mg/m² Day 1-14), or low-dose melphalan (2mg/d), used to be applied to patients with advanced MDS due to a lack of better alternatives in the past, or were tested in small, mostly phase-II studies. Because of the demethylating agents now available non-intensive chemotherapy as a primary therapy of high-risk MDS will become less important in the future. Such treatment will present a reasonable alternative in the individual case if other options are exhausted, for example, epigenetic therapy (evidence strength IIa, recommendation level B).

6.5 Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is as yet the only potentially curative treatment for MDS. By improving supportive measures and/or reducing the intensity of conditioning, we have recently succeeded in extending the indication to patients who are up to 70 years old. This method still continues to be an individual procedure particularly in patients > 60 years. Each eligible MDS patients should therefore be presented to a transplant center as soon as the diagnosis is confirmed (evidence strength 4, recommendation level D) [22].

6.6 Summary

The option of an allogeneic stem cell transplantation should be initially considered for all patients with high-risk MDS. All patients who do not qualify for this therapy should undergo treatment with 5-azacytidine. If the disease progresses, the patients should be included in clinical trials, whenever possible.

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10 Active Studies

www.mds-register.de

11 Systemic Therapy- Protocols

- [Myelodysplastisches Syndrome - Systemic Therapy - Protocols](#)
- [Myelodysplastisches Syndrome - Systemic Therapy - Protocols](#)

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13 Disclosures

according to the rules of the German Association of Hematology and Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.

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|-------------|---|--|---------------|--------------------------------|---|---|--|
| Hofmann | The State of Baden-Württemberg Land Berlin (until 2009) | - | - | - | Amgen, Celgene, Novartis | Amgen, Celgene, Novartis | - |
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