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Swiss Medical Forum

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Recommendations for the Diagnosis and Treatment of Myelodysplastic Syndromes in Adult Patients in Switzerland

Swiss Society of Hematology

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EMH Editions médicales suisses SA
Editores Medicorum Helveticorum

Recommendations for the Diagnosis and Treatment of Myelodysplastic Syndromes in Adult Patients in Switzerland

Swiss Society of Hematology¹

Quintessence

- Myelodysplastic syndrome (MDS) should be suspected in elderly patients presenting with refractory anaemia or other cytopenias, fatigue, bleeding and infection.
- Even for elderly patients with MDS treatment options are available that significantly increase quality of life and prolong survival, and can be cost efficient.
- Optimal treatment strategies require diagnostic work-up and assessment of the individual risk status based on defined criteria (WHO classification, IPSS-Score), mainly blood/bone marrow cell counts, number of cytopenias, bone marrow morphology and cytogenetics, transfusion requirements, as well as comorbidity.
- Treatment strategies include best supportive care (transfusions, growth factors, iron chelation, anti-infectives), treatment aiming to improve blood cell counts (immunomodulation/-suppression, epigenetic therapy), and treatment aiming to change the natural history of the disease (epigenetic therapy, chemotherapy and/or haematopoietic stem cell transplantation).

Introduction

The disease often begins with unspecific symptoms like fatigue and usually hyporegenerative and macrocytic anaemia, and persists after vitamin supplementation, hence the term refractory anaemia. Other cell lineages can be affected from the beginning, too (neutropenia with infections, thrombocytopenia with haemorrhages). Examination of the blood smear may show signs of dysplasia in one or several cell lineages. These patients show a wide variation in disease evolution. Most cases occur *de novo* but some patients may present with secondary MDS after cytotoxic treatment for malignancy.

MDS is a preleukaemic disease and patients die either of acute leukaemic transformation (30–40%) or consequences of cytopenias. MDS is a frequent, malignant haematological neoplasia (haematological neoplasias being generally rare) with a median age at onset of 68 years. Based on German data (Düsseldorf registry [1]) an overall yearly incidence of about 300 new cases must be expected. More cases of MDS are to be expected due to a demographic shift to higher age.

The MDS is a clonal disorder characterised by the paradoxical coexistence of abnormal “growth” and “death” in the bone marrow (ineffective haematopoiesis). The underlying causes are unknown, but genetic alterations in haematopoietic progenitor cells play a dominant

role, while reactions in the marrow stroma and the immune system contribute (see Tefferi [2]).

This review, produced by a Swiss consensus group, is motivated by developments in diagnosis, classification of the disease, prognostication and therapy. The purpose of this article is to give recommendations for diagnosis and treatment of adult patients with MDS.

Diagnosis

Diagnosing MDS requires a thorough clinical work-up. Sometimes it is not possible to make a definitive diagnosis of an MDS at first presentation. In such cases clinical observation of the patient as well as a repeated work-up 4 to 6 months later should allow to come to a definitive conclusion.

General aspects

In case of a suspicion of an MDS, the diagnostic strategy aims to

- make the distinction between reactive changes and myeloid neoplasm;
- perform subclassification of the MDS;
- assess the risk score of the MDS;
- distinguish between primary and secondary MDS.

Diagnostic tools and most relevant findings

The *clinical history* of the patient and his family belongs to the diagnostic procedure (history of cytopenia, number of transfusions, and prior exposure to cytotoxic drugs or radiation therapy).

The *clinical investigation* should search for organomegaly or organ infiltration (liver, spleen, lymph nodes, skin infiltration, mucosal infiltration, etc.), bleeding manifestations and infections.

The *laboratory methods* required for diagnosing and monitoring MDS are given in table 1 [↩](#). Bone marrow examination is the back bone of the diagnostic work-up. In each case cytology and histology should be performed. In case of discrepancy between both analyses,

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This work was supported by an unrestricted grant from Celgene GmbH.

M.S. and C.T. are members of an advisory board of Celgene GmbH.


Table 1. Procedures essential for diagnosing and monitoring MDS.

Material	Technology	Tests	Comments
Peripheral blood	Haematology	Cell count	with special attention to: Macrocytosis, erythroblasts with or without dyserythropoiesis
		Erythrocyte indices	Pseudo-Pelger forms of the neutrophils, pyknotic neutrophils, neutrophil granularity, immature myeloid precursors, abnormal monocytes, blast cells (with or without Auer rods)
		Reticulocyte count	Anisocytosis of the platelets, abnormal platelets (granularity).
		Smear	
	Clinical Chemistry	Liver function tests	A thorough clinical work-up is essential.
		Kidney function tests	
		Thyroid work-up	
		Ferritin (Transferrin saturation)	
		Vitamin B ₁₂	
		Red cell folate (serum folate in case of a transfused patient)	
HIV			
Serum erythropoietin level (EPO)			
Peripheral blood and/or Bone marrow	Cytochemistry	PAS staining	Cytochemistry can be helpful in assessing dysplasia of erythroid (PAS), myeloid (POX) and monocytic (NSE) cell lines.
		Peroxidase staining (POX)	
	Non-specific esterase staining		
Flow-cytometry		may be useful to assess overexpression (CD56), aberrant expression (CD2) or underexpression (CD16, CD10, etc.) of neutrophils and monocytes. These changes can be interpreted as a dysplastic feature.	
	PNH	Research of a paroxysmal nocturnal haemoglobinuria clone on neutrophils should be performed, particularly in hypoplastic MDS.	
Bone marrow	Cytology	Standard staining	informs mainly about the morphology of the individual cells and the blast counts; a differentiation of 500 cells in different parts of the smear should be performed. Dysplasia of each cell line should be quantified (cut-off 10% dysplasia by cell line), as well as the ringed sideroblasts in iron staining (cut-off 15% of all erythroblasts).
		Iron staining	
	Histology	Standard staining	informs mainly about the topography of the cells and the myelofibrosis. A significant degree of myelofibrosis is observed in approximately 10% of the MDS. These cases are referred to as MDS with fibrosis (MDS-f). Histology can assess the clustering and/or abnormal localisation of the cells (micro-megakaryocytes, ALIPS, CD34+ cells). Immunohistochemistry (CD34 and/or CD117) is useful to quantify the number of "blasts".
		Immunohistochemistry	
	Cytogenetic analysis	conventional	is mandatory;
		FISH	FISH analysis may provide useful additional information.


due to different sampling/method, the worst result should be taken into consideration for further patient management.

Cytogenetic features

Cytogenetic abnormalities are seen in nearly 50% of *de novo* MDS and in 80–90% of therapy-related cases. There is an enormous variability of cytogenetic abnormalities. Cytogenetic changes noted in MDS mainly consist of unbalanced abnormalities, including partial or total chromosome gains or losses. The most frequently occurring gain of genetic material is trisomy 8. The commonest abnormality in MDS is loss of genetic material as a result of whole or partial monosomies (chromosome 7, Y, and deletions 5, 7 and 20).

A recent study of 2072 patients with MDS revealed that 59% of all 2370 genetic abnormalities observed in 1080 patients occurred with a frequency of less than 2% [3]. Chromosome abnormalities can occur as single defect, or as part of complex defects (≥ 3 changes; unfavourable prognosis) (fig. 1 .

Risk stratification and classification

The World Health Organization has defined criteria for diagnostic categories of MDS [4] (table 2 ). Prognostic scores aid to define therapeutic indications. The main prognostic factors are patient age, the number of cell lineages with cytopenia (anaemia, thrombocytopenia, neutropenia), the blast count, the cytogenetic findings, comorbidity, and the need for

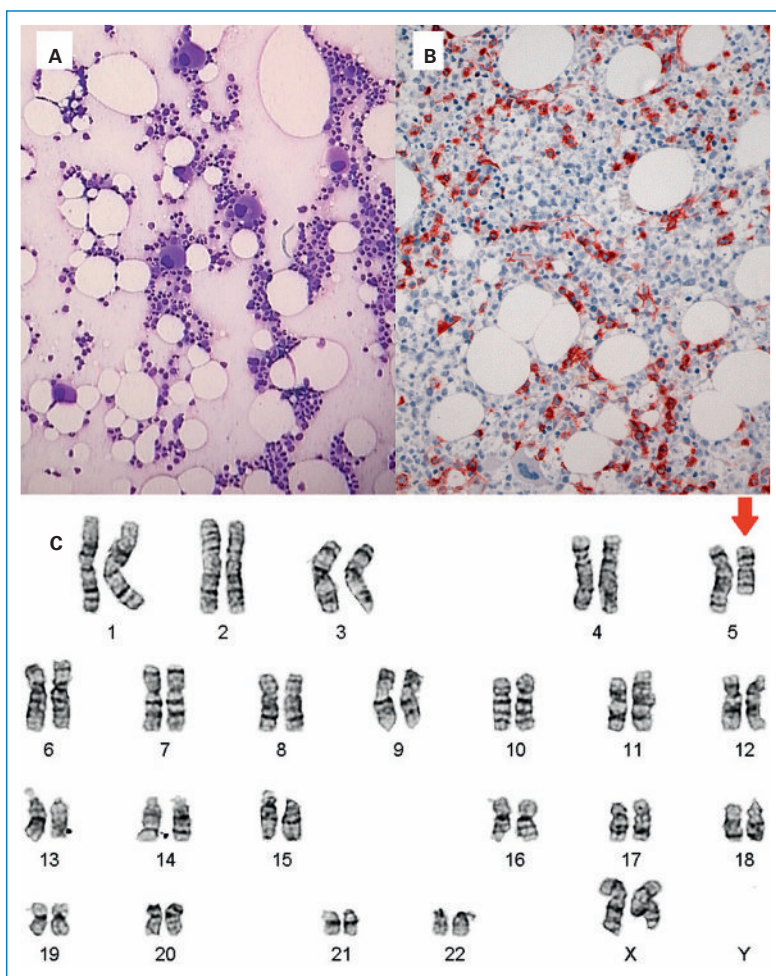


Figure 1

Illustration of morphological (A), immunohistochemical (B) and cytogenetic (C) findings in MDS.

- A** Isolated deletion (5q). The patient has anaemia with marked macrocytosis (MCV 120 fl) and moderate thrombocytosis (platelet count $504 \times 10^9/l$). In the bone marrow smear, the megakaryocytes are increased in number, and most of the megakaryocytes are middle sized with hypolobated, rounded nuclei. MGG staining, $\times 100$.
- B** Patient with refractory anaemia with excess blasts-2 (RAEB2). The bone marrow biopsy is hypercellular and shows alteration of the normal histotopography. There is an increase in immature/blastoid cells that are highlighted by immunohistochemical staining for CD34 (about 15%). Blasts in RAEB tend to form cell clusters that are located away from bone trabeculae, i.e., abnormal localised immature precursors (ALIP). CD34-immunohistochemistry, $\times 63$.
- C** Karyotype: 46,XX,del(5)(q13q33), bone marrow, G-banding.

transfusions. Based on this knowledge two risk scores have been proposed:

- The *International Prognostic Scoring System (IPSS)* for MDS allows the assessment of an individual patient's prognosis beyond age and comorbidity [5]. It is based on the number of cytopenias (0–1 versus 2–3 cell lineages), the percentage of blasts in the bone marrow smear (<5%, versus 5–10%, versus 11–20% versus 21–30%) and cytogenetic criteria (karyotype: good versus intermediate versus poor). Using this score, patients are subdivided into risk groups as shown in table 3 [6]. The prognostic value has been confirmed in prospective studies.
- The *WHO-based Prognostic Scoring System (WPSS)* for MDS uses WHO MDS subtypes diagnosis (RA, RARS, 5q; RCMD, RCMD-RS; RAEB-1; RAEB-2), karyotype, and need for transfusions.

A coarse partition allows for a distinction between low-risk MDS (predominantly cytopenia, low blast count) and high-risk MDS (elevated blast count, predominantly leukaemic transformation).

Pathophysiology

The mechanisms causing MDS are not understood, but involve abnormalities in the self-renewal and differentiation of haematopoietic progenitor cells. This leads to uncontrolled and uncoordinated proliferation and apoptosis, and hence to distorted proportions of various dysplastic cell lineages in the bone marrow and the peripheral blood.

At the source of any MDS is one or more genomic alteration in haematopoietic bone marrow stem cells. Transcription factors and secondary signal (receptor) proteins may also be affected, giving an abnormal clone a growth advantage over its normal counterpart. The involvement of T lymphocytes contributes to autoimmune phenomena seen in about 10% of MDS patients. The genetic instability contributes to the evolution of MDS into AML. Accordingly, various molecular alterations have been reported in MDS that affect genes involved in mitotic check-points, cell-cycle control and growth factor receptors. Apart from the 5q-syndrome that is characterised by a clear genotype–phenotype relationship, no specific clinico-cytogenetic entity has been reported. MDS with 5q deletions respond well to treatment with immunomodulators. In secondary MDS, unbalanced abnormalities involving chromosome 5 and 7 commonly occur after exposure to alkylating agents (e.g., melphalan, cyclophosphamide), and alterations of the MLL gene located at 11q23 are generally seen after previous treatment with topoisomerase inhibitors (e.g., etoposide).

Treatment

Aims

Treatment of MDS should aim to alleviate cytopenia, delay leukaemic transformation, prolong survival, and optimise quality of life. The only potentially curative treatment is allogeneic haematopoietic stem cell transplantation, which is available only for a minority of patients and, due to its toxicity, not a reasonable choice for most of the patients with low-risk disease. The challenge of MDS treatment lies in choosing a tailored strategy for each patient, taking into account age, general health condition, comorbidities, disease type, time since diagnosis, and prognostic score.

These Swiss recommendations are adapted from the guidelines of the (American) National Comprehensive Cancer Network (NCCN, fig. 2 [7], [v.1.2010, MDS-5 and MDS-6 of ref. 6]).

For the assessment of MDS treatment outcome an International Working Group (IWG) has defined criteria of five aspects of response based on treatment goals [7, 8]. The response criteria depend on two different aims of the treatment:

Table 2. Diagnostic classification criteria (WHO 2008) [4].

WHO Category		Peripheral blood	Bone marrow
RCUD (RA, RN, RT)	Refractory cytopenias with unilineage dysplasia, including refractory anaemia, refractory neutropenia and refractory thrombocytopenia	Uni-, or bicytopenia	Unilineage dysplasia: $\geq 10\%$ of cells in 1 myeloid lineage; $< 5\%$ blasts.
RARS	Refractory anaemia with ring sideroblasts	Anaemia no blasts	$\geq 15\%$ of erythroid precursors with ring sideroblasts; Erythroid dysplasia only; $< 5\%$ blasts.
RCMD	Refractory cytopenia with multilineage dysplasia	Cytopenia(s) $< 1 \times 10^9/l$ monocytes	Dysplasia in $\geq 10\%$ of the cells; in ≥ 2 myeloid lineages; $< 5\%$ blasts; $\pm 15\%$ ring sideroblasts.
RAEB-1	Refractory anaemia with excess blasts-1	Cytopenia(s) $\leq 2-4\%$ blasts $< 1 \times 10^9/l$ monocytes	Unilineage or multilineage dysplasia; 5–9% blasts; no Auer rods.
RAEB-2	Refractory anaemia with excess blasts-2	Cytopenia(s) 5–19% blasts $< 1 \times 10^9/l$ monocytes	Unilineage or multilineage dysplasia; 10–19% blasts; \pm Auer rods.
MDS-U	Myelodysplastic syndrome unclassified	Cytopenias	Unilineage dysplasia or no dysplasia but characteristic cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS. $< 5\%$ blasts.
MDS with del(5q)	Myelodysplastic syndrome associated with isolated del(5q)	Anaemia Normal or elevated platelet count	Unilineage erythroid dysplasia; isolated del(5q); $< 5\%$ blasts.

- Treatment altering the natural history of the disease.

The response criteria include:

- a) specific criteria of peripheral blood and bone marrow on two successive assessments;
- b) response parameters of the peripheral blood must be sustained for at least 8 weeks.

The response categories are complete remission, partial remission, stable disease, relapse, and disease progression. Additionally, cytogenetic response (complete, partial) is defined.

- Haematological improvement:

Haematological improvement aims to improve quality of life of the patients without necessarily changing the natural course of the disease.

The response criteria are based exclusively on haematological response of peripheral blood. Depending on the type of treatment, one, two or all three cell lineages can show improvement. Therefore, the haematological improvement can be an erythroid response, a platelet response and/or a neutrophil response.

Best supportive care (BSC)

Best supportive care is an option for low-risk patients and for higher risk patients who are not eligible for more intensive therapy. The aims of BSC are alleviation of cytopenias and maintaining quality of life. This can be achieved by transfusions of erythrocytes and platelets. Erythropoiesis-stimulating agents (ESAs) or granulocyte colony-stimulating factor (G-CSF) have the potential to improve the blood values by stimulation of particular bone marrow functions.

An important issue is the treatment of iron overload for patients with a good prognosis.

Transfusion – Erythrocytes

The target level of haemoglobin to be maintained by red blood cell transfusions is 80–100 g/l. However, the transfusion limits have to be set according to the individual situation. On the one hand many patients develop a good tolerance to haemoglobin values below 80 g/l, on the other hand elderly and comorbid patients may have a reduced tolerance to anaemia. After allogeneic HSCT all cellular transfusion products must be irradiated for life-time.

Transfusion – Thrombocytes and Granulocytes

During an active treatment strategy prophylactic platelet transfusions are administered to patients without additional bleeding risk if the platelet count falls below $10 \times 10^9/l$. Transfusions only in case of relevant bleeding are an option for patients under BSC. Febrile infections afford special attention, since they are accompanied by increased platelet consumption. The decision for prophylactic platelet transfusion must be made individually.

Granulocyte transfusions are not recommended in patients with MDS.

Growth factors

Patients with haemoglobin levels below 100 g/l and serum erythropoietin levels below 300 mU/ml may be considered for ESAs. The dosage required in MDS is higher than in renal anaemia. A response to ESAs is observed in about one third of MDS patients. In order to minimise the risk of thromboembolic and other complications, the target haemoglobin levels after treatment with ESAs should not exceed 110 g/l. If there is no response after 4–8 weeks, the treatment

should be discontinued. In our experience, patients with serum erythropoietin levels >300 mU/ml rarely respond. G-CSF administration is not a treatment of severe neutropenia in MDS if the patient has no infection. MDS pa-

tients with $<0.5 \times 10^9/l$ neutrophils are candidates for G-CSF therapy in case of recurrent infections. The dose and treatment interval of G-CSF has to be chosen individually, in many patients 1–3 injections per week may be sufficient.

Table 3. The modified definition of the IPSS for newly diagnosed MDS [5]. The individual IPSS risk can be calculated by adding the score values for bone marrow blasts, numbers of cytopenias and cytogenetic risk groups.

Bone marrow blasts	Number of cytopenias	Cytogenetic risk group karyotype	IPSS Score
<5%	0–1	Low normal, isolated -Y, isolated del(5q) or isolated del(20q)	0
5–10%	2–3	Intermediate all other abnormalities	0.5
–	–	High ≥3 abnormalities or chromosome 7 abnormalities	1.0
11–20%	–	–	1.5
21–30%	–	–	2.0
Overall score (added up IPSS scores from above)	IPSS risk group	Median survival (no therapy)	25% progression to AML (no therapy)
0	Low	LOW	9.4 years
0.5–1	Intermediate I	INT-1	3.3 years
1.5–2	Intermediate II	INT-2	1.1 years
≥2.5	High	HIGH	0.2 years

Cytopenia: platelets <100 000/μl, haemoglobin <10 g/dl, ANC <1500/μl; cytogenetics: low, intermediate or high risk.

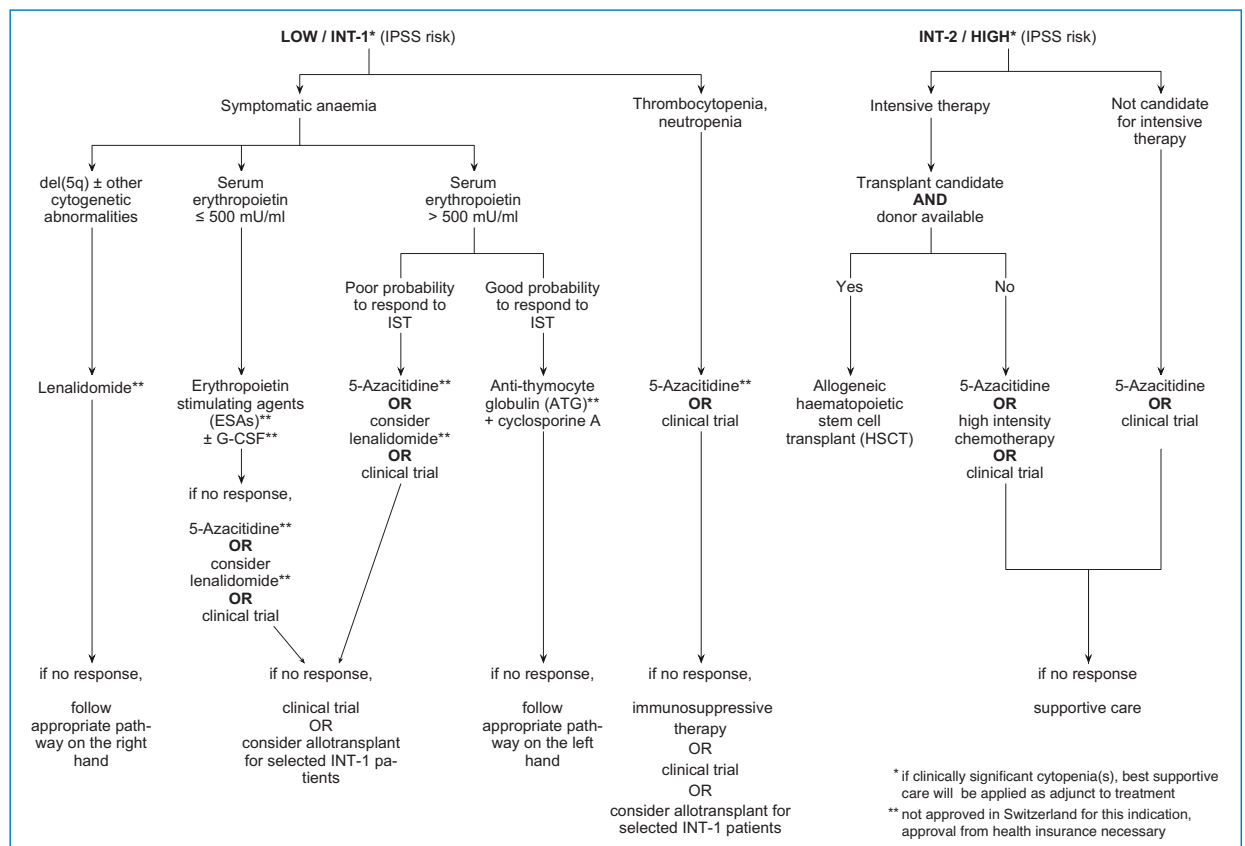


Figure 2

NCCN Guidelines for the therapy of MDS [v.1.2010, MDS-5 and MDS-6 of ref. 6]. For Switzerland the authors recommend a lower serum erythropoietin threshold of 300 mU/ml (immunosuppressive treatment [IST]).

In Switzerland ESAs and G-CSF are not approved for supportive care of patients with MDS. This means that the health insurance must approve growth factor administration prior to treatment.

Androgens such as danatrol may also reduce transfusion dependency. In selected cases low dose steroids may be helpful against symptoms of inflammatory reactions.

Iron chelation

Chronically transfused patients will develop iron overload and organ damage (heart, liver, endocrine glands). The decision for iron chelation should be based on the patient's life expectancy and red cell transfusion need. Candidates are mainly patients with low-risk MDS with a median survival of 3–6 years, and bone marrow transplant candidates. The therapy should be considered as soon as the patients have received at least

Characteristic for MDS is a paradoxical coexistence of abnormal "growth" and "death" in the bone marrow

20 units of red blood cell transfusions or if the serum ferritin levels exceed 1000 µg/l. The thresholds and the benefit of iron chelation therapy are discussed

controversially. Available iron chelators are the longstanding compounds deferoxamine (subcutaneous infusion with a pump) and deferiprone (risk of severe neutropenia). Nowadays the treatment of choice for the majority of patients is deferasirox, which is administered orally once daily. Under treatment serum ferritin levels should be monitored every 3 months.

Anti-infectious agents

Neutropenia and granulocyte dysfunctions make MDS patients vulnerable to infections with gram-positive and gram-negative bacteria and with fungi. In case of febrile infections in patients with neutrophil counts $<0.5 \times 10^9/l$ empirical broad spectrum antibiotic therapy should be initiated. If fever persists, invasive aspergillosis must be ruled out by CT-scan.

Vaccinations against influenza virus or varicella zoster virus should be considered according to respective guidelines. In selected patients with recurrent infections and neutropenia prophylactic antibiotics may be useful.

Treatment of cytopenia (LOW and INT-1 risk patients)

The NCCN recommendations (fig. 2) for low-risk patients (IPSS: LOW and INT-1) propose first-line treatment as well as subsequent lines of treatment to be customised to previous treatment response [6]. In any situation, such decisions should be influenced both by the severity of the haematological disease and by the patient's condition. It should also be evaluated whether a patient's impaired condition is reversible, and whether it is caused by the disease itself – with the hope of reversibility when the MDS is treated – or due to other comorbidities that may persist or need to be treated as well. HSCT should be considered in selected MDS patients not responding to therapy.

Therapies including immunosuppressants, modifiers of biologic response, milder forms of chemotherapy, and

the recently developed hypomethylating agents should be discussed.

Symptomatic anaemia treatment depends on cytogenetic evaluation and serum erythropoietin levels, as well as response to any treatment attempt (fig. 2), see under "Best supportive care" (BSC).

Immunosuppressive therapy (IST)

Anti-thymocyte globulin (ATG) and cyclosporine A (CSA) should be considered as first-line treatment in patients younger than 60 years with hypocellular bone marrow and symptomatic anaemia associated with serum erythropoietin levels exceeding 300 mU/ml. The presence of the HLA-DR15 antigen, a PNH clone or a chromosome abnormality (e.g., trisomy 8) may also be selection criteria. As this treatment intermittently deteriorates cytopenias, it is only performed in specialised centres.

Immunomodulation therapy

Lenalidomide is the first-line treatment of symptomatic anaemia in MDS with 5q deletion without excess of blasts and with or without associated cytogenetic abnormalities.

Lenalidomide is administered at 10 mg/day in cycles of 21 days every four weeks. Lenalidomide may cause cytopenias requiring to dose reduction. In Switzerland lenalidomide (Revlimid®) is assigned "orphan indication" status for the treatment of MDS by Swissmedic, and is reimbursed by the compulsory health insurance ("OKP") only after approval by the insurer's independent examining physician ("Vertrauensarzt").

Epigenetic therapy

Hypomethylating agents (e.g., 5-azacitidine) may be used in patients with progressing low-risk disease or patients refractory to other treatments as shown in table 3 (defining a "high-risk group" within this category). Alternative and novel therapeutic approaches, e.g., with histone deacetylase inhibitors (HDACI, e.g., valproic acid or vorinostat) are being developed.

Treatment of evolution to leukaemia (INT-2 and HIGH risk patients)

Patients with advanced disease may respond to leukaemia type chemotherapy, and remission rates up to 40–60% have been described. Remissions only rarely last for several years and most patients will relapse after a variable period of time. Palliative cytoreductive treatments with hydroxyurea, etoposide, idarubicin or cytosine arabinoside (Ara-C) are common. Similarly to stem cell transplantation, age and comorbidity greatly influence indication and success rate of high-intensity therapy.

Haematopoietic stem cell transplantation

The mainstay of intensive therapy for higher risk patients (IPSS: INT-2 and HIGH) is allogeneic HSCT. NCCN recommendations (fig. 2) make decisions for intensive therapies dependent on the individual clinical situation (age, comorbidity, tolerance to adverse effects) and the availability of a suitable donor [6].

For all MDS patients, haematopoietic stem cell transplantation is the only curative treatment option. Allogeneic HSCT is most often performed, but (experimental) autologous transplantation may also be feasible in selected younger patients.

Epigenetic therapy

Hypomethylating agents, e.g., 5-azacitidine, a methyltransferase inhibitor that was shown to decrease the leukaemia potential and prolong survival in MDS patients [9], is a first-line treatment for patients with an excess of blasts and/or complex karyotypic anomalies, and may also be used in patients with bicytopenia alone. 5-Azacitidine is administered in at least four cycles (given subcutaneously at 75 mg/m² for 7 of 28 days). More than four cycles may be needed for complete or partial response. 5-Azacitidine is the only hypomethylating agent approved in Switzerland.

Pharmacoeconomic Aspects

It appears that some elderly patients are denied adequate modern therapies because of cost and/or reimbursement concerns. It is evident that novel drugs, such as 5-azacitidine, lenalidomide, ATG, ESAs and growth factors, are expensive. However, maintaining patients on BSC, including transfusions of red cells and platelets, as well as iron chelation therapy, is burdensome for the healthcare system and not necessarily less expensive. Exact figures for comparative cost-effectiveness are difficult to calculate, and are not available for Switzerland.

Another important aspect is that reducing transfusion needs will also improve patients' quality of life.

Authors' contribution

JP chaired the Swiss Consensus Board on MDS. All authors contributed to the conception of the manuscript and supported the preparation of the manuscript.

All authors have read and approved the final manuscript.

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The complete numbered reference list can be found at www.medicalforum.ch.