Guidelines for the diagnosis and treatment of Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

Nordic MDS Group

Issue 6

5th update, 1st of December 2011

Introduction

The myelodysplastic syndromes (MDS) encompass a heterogeneous group of malignant bone marrow diseases characterized by ineffective, dysplastic hematopoiesis with subsequent pancytopenia, and an increased risk for developing acute myeloid leukemia (AML). There is a vast variation in symptoms and prognosis. While some patients may live for decades with mild asymptomatic anemia, others present with profound pancytopenia and rapid progression towards AML. Several potential therapeutic options for MDS have been evaluated in clinical trials, but the majority of these have shown only moderate efficacy. Moreover, there are relatively few randomized controlled trials to support decision-making for the individual patient. The Nordic MDS group (NMDSG) is a pan-Nordic organisation, which has conducted clinical trials in MDS since 1985. NMDSG decided, in 2003, to write guidelines for the diagnosis and management of MDS, which will be published on-line at the website www.nmds.org. The Guidelines are written for health professionals with a speciality or an interest in hematology. It will be updated at least every second year, and we therefore recommend colleagues to use the on-line version, rather than to print and copy paper versions of the document.
The first version was published at www.nmds.org in November 2004. The present version, issue #6, constitutes the fifth update.

Nordic MDS Group 1st of December, 2011.

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News in issue 6

All chapters have been rewritten taking into account novel knowledge from recent publications. More specifically the following changes can be mentioned:

- The importance of considering rare familial forms of MDS including telomere disorders has been stressed in the diagnostic section. In the section on prognosis, newer cytogenetic risk groups are described.
- The paragraph describing iron chelation has been rewritten, with a common background section and more details regarding a large prospective trial evaluating deferasirox in iron overloaded MDS patients.
- Alemtuzumab has been added as a potential alternative to ATG treatment in low risk MDS.
- The hematopoietic cell transplantation comobidity index by Sorror and coworkers has been included in the section on allogeneic SCT.

Evidence levels and recommendation grades

Where possible and appropriate, recommendation grade (A, B and C) and evidence level (I – IV) are given (for definitions see Table 1). Grade A does not imply that a treatment is more recommendable than a grade B, but implies that the given recommendation regarding the use of a specific treatment is based on at least one randomised trial.

Table 1.

A) Levels of evidence

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports and/or clinical experiences of respected authorities

B) Grades of recommendation

Grade	Evidence level	Recommendation
A	Ia, Ib	Required: At least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required: Availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C	IV	Required: Evidence obtained from expert committee reports or opinions and /or clinical experiences of respected authorities. Indicates absence of directly applicable studies of good quality

Diagnostic workup of suspected MDS

The diagnosis of MDS rests largely on morphological findings of bone marrow dysplasia in patients with clinical evidence of impaired hematopoiesis manifested by different combinations of anemia, neutropenia and thrombocytopenia. The diagnostic criteria should distinguish MDS from reactive causes of cytopenia and dysplasia as well as from other clonal stem cell disorders. In younger individuals (<50 years) one must also consider the rare possibility of congenital or hereditary conditions, especially if a positive family history, concomitant physical abnormalities (ex nail dystrophy, facial abnormalities) or unexplained liver/pancreas/pulmonary affections. These conditions include Congenital Dyserytropoietic Anemias (CDA), Telomere-associated syndromes including Congenital Dyskeratosis, Hereditary Sideroblastic Anemia, Fanconi Anemia (FA), Congenital Neutropenias (Kostmann, Schwachman-Diamond) and Diamond-Blackfan Anemia (DBA).

Diagnostic work-up of MDS:

Patient history and examination:
This should include family history, prior chemotherapy and irradiation, occupational exposure, concomitant medication, tendency for bleeding/bruising and infection, and a complete physical examination including spleen size. In younger patients, family history should include, if possible, two generations back and encompass not only haematological but also other familiar accumulation of symptoms.

Blood tests:
- WBC, differential, hemoglobin, platelet count, red blood cell indices (MCV, MCHC, RDW) and reticulocyte count. For dysplasia, see below under bone marrow evaluation.
- Homocysteine, if elevated ≥ 25-30 µmol/L and normal renal function: measure RBC-folate/S-folic acid, and serum cobalamins. Hematologically significant cobalamin/folate deficiency usually causes homocysteine > 30 (twice the upper reference limit). In such cases, response to adequate vitamin therapy is: falling transferrin saturation within 24h, increased reticulocytes d5-6, increasing Hb, decreasing MCV in 2-3 weeks.
- Iron, transferrin (TIBC), ferritin, LDH, bilirubin, haptoglobin, DAT (Coombs test), ALAT, ASAT, Alkaline phosphatase, albumin, uric acid, creatinine, S-erythropoietin, S- protein electrophoresis (S-immunoglobulins).

- Screening for HIV, Parvovirus B19 (hypoplastic MDS). Screening for hepatitis B and C in transfusion dependent patients.
- If suspicion of telomere-associated disease, please contact regional coordinator for advice concerning analysis of telomere length and specific mutations.

Bone marrow analysis:
A diagnosis of MDS usually necessitates repeat bone marrow examinations a few weeks or months apart in order to firmly establish the diagnosis and to identify cases with rapid disease progression We recommend evaluation of bone marrow morphology, and dysplasia of blood and bone marrow cells according to the WHO 2008 classification

- Bone marrow aspirate and biopsy.

For significant dysplasia, dysplastic features should be present in at least 10% of the nucleated cells in the lineage in consideration. At least 500 marrow cells and 200 cells in blood should be evaluated and an optimal staining of blood and marrow slides is important. The presence of pseudo-pelger neutrophils, ring sideroblasts, micromegakaryocytes and increased blast count show the strongest correlation with clonal markers in MDS.

- According to the WHO classification, a cytogenetic analysis should be done in all cases even in the very elderly to ensure a complete diagnostic and prognostic procedure.
- A flow cytometric analysis ($CD34^+$ cell count) is relevant in high-risk disease.

In some patients meaningful cytopenias can be present without any other obvious cause, significant dysplasia or bone marrow blast increase. This condition has been proposed to be called ICUS (Idiopathic Cytopenias of Undetermined Significance). These patients should be carefully monitered since a fraction of them will develop decisive MDS criteria. Thus, a presumptive diagnosis of MDS can be made in the absence of significant dysplasia or bone marrow blast increase, if typical chromosomal abnormalities are present or are developed.

Differential diagnosis:
The diagnosis of MDS may be difficult, in particular in patients with less than 5% bone marrow blasts and only one cytopenia. No single morphologic finding is diagnostic for MDS and it is important to keep in mind that MDS sometimes remains a diagnosis of exclusion. For this reason, thorough work-up to rule out the possible differential diagnoses below is recommended.

- B12 / folate deficiency
- Recent cytotoxic therapy
- HIV infection
- Anemia of chronic disorders (infection, inflammation, cancer)
- Autoimmune cytopenia
- Chronic liver disease
- Excessive alcohol intake
- Exposure to heavy metals
- Drug-induced cytopenias
- Other stem cell disorders incl. acute leukaemia (with dysplasia or Fab type M7), aplastic anemia, myelofibrosis (in case of MDS with marrow fibrosis) and paroxysmal nocturnal hemoglobinuria.

Classifications

The Nordic MDS group recommends classification according to WHO 2008 only

WHO 2008 classification of MDS

Peripheral blood and bone marrow findings in myelodysplastic syndromes

Disease	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage dysplasia (RCUD) Refractory anaemia (RA) Refractory neutropenia (RN) Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia[1] No or rare blasts (<1%)	Unilineage dysplasia; ≥ 10% of the cells of the affected lineage are dysplastic <5% blasts <15% of the erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia only ≥ 15% of erythroid precursors are ring sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1%)[2] No Auer rods <1x10^9/l monocytes	Dysplasia in ≥ 10% of cells in two or more myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts No Auer rods ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenia(s) <5% blasts No Auer rods <1x10^9/l monocytes	Unilineage or multilineage dysplasia 5-9% blasts[2] No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5-19% blasts Auer rods ±[3] <1x10^9/l monocytes	Unilineage or multilineage dysplasia 10-19% blasts Auer rods±
Myelodysplastic syndrome – unclassified (MDS-U)	Cytopenias ≤ 1% blasts[2]	Unequivocal dysplasia in less than 10% of cells in one or more myeloid cell lines <5% blasts[2]
MDS associated with isolated del(5q)	Anaemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No auer rods

[1] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U
[2] If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB-1. If the marrow myeloblast percentage is <5% and there are 1% myeloblasts in the blood, the case should be classified as MDS-U.
[3]Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2

WHO classification 2008 of myelodysplastic/myeloproliferative neoplasms

Disease	Blood findings	Bone marrow findings
Chronic myelomonocytic leukaemia (CMML)	Peripheral blood monocytosis > $1x10^9$/l No BCR/ABL-1 fusion gene <20% blasts	Dysplasia in one or more myeloid lineage[1] <20% blasts. Blasts include myeloblasts, monoblasts and promonocytes. No rearrangement of PDGFRA or PDGFRB
Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)	Leukocytosis, neutrophilia Neutrophilic dysplasia Neutrophil precursors ≥10% of leukocytes Blasts <20% No BCR-ABL1 fusion gene No rearrangement of PDGFRA or PDGFRB Minimal basofilia Monocytes < 10% of leukocytes	Neutrophil dysplasia with or without dysplastic lineages <20% blasts
Juvenile myelomonocytic leukaemia (JMML)	Peripheral blood monocytosis >$1x10^9$/l <20% blasts Usually WBC > $10x10^9$/l	<20% blasts. Evidence of clonality
Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN)	Mixed MDS and MPN features No prior diagnosis of MDS or MPN No history of recent growth factor or cytotoxic therapy to explain MDS or MPN features No BCR-ABL1 fusion gene of rearrangements of PDGFRA or PDGFRB	Mixed MDS and MPN features <20% blasts
[1]Refractory anaemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) (provisional entity)[2]	Persistent thrombocytosis >$450x10^9$/l Anaemia BCR-ABL1 negative Cases with t(3;3)(q21;q26), inv(#)(q21q26) and isolated del(5q) are excluded	Morphologic features of RARS; ≥ 15% of erythroid precursors are ring sideroblast Abnormal megakaryocytes similar to those observed in BCR-ABL1 negative MPN

[1] If myelodysplasia minimal or absent, CML can still be diagnosed if the other requirements are met and there is ann acquired clonal cytogenetic or molecular geneticabnormalityBicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U

[2] If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB-1. If the marrow myeloblast percentage is <5% and there are 1% myeloblasts in the blood, the case should be classified as MDS-U.

[3]Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2

Prognosis

MDS is a very heterogenous disease both from a pathogenetic, clinical and prognostic viewpoint. IPSS is the most widely used prognostic model but it has several limitations. It is based on untreated, de novo MDS at diagnosis and exludes s/t-MDS and CMML with leukocyte count >12 $x10^9$/l. This is also true for WPSS which however is a dynamic score also including transfusion dependency as an independent poor prognostic variable. Importantly, IPSS also underestimates the prognostic impact of karyotype relative to the percentages of blast cells in the bone marrow.

IPSS for MDS (International Prognostic Scoring System)

(Greenberg et al, 1997)

All patients with MDS have a reduced life expectancy compared to age matched controls. The IPSS is a multivariate analysis of a largely untreated patient population of 816 patients used to evaluate the prognosis of newly diagnosed MDS patients.

All patients (n=816):

Risk group	Score	Median survival (years)	Time to AML transformation (for 25% in years)
Low risk	0	5.7	9.4
INT-1	0.5-1.0	3.5	3.3
INT-2	1.5-2.0	1.2	1.1
High risk	≥2.5	0.4	0.2

Patients below age 60 (n=205):

Risk group	Score	Median survival (years)	Time to AML transformation (for 25% in years)
Low risk	0	11.8	>9.4
INT-1	0.5-1.0	5.2	6.9
INT-2	1.5-2.0	1.8	0.7
High risk	≥2.5	0.3	0.2

Score value

Prognostic variable	0	0.5	1	1.5	2
BM blasts (%)	<5	5-10	-	11-20	21-30
Karyotype°	Good	Intermed.	Poor		
Cytopenias*	0/1	2/3			

° Good: normal, -Y, del(5q), del(20q). Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities. * Hemoglobin <100 g/l, ANC <1.8 x 10^9/l, platelets <100 x 10^9/l.

Low risk vs High risk MDS

In daily clinical practice, MDS is divided into so-called ”low risk” MDS encompassing IPSS low risk and INT-1, whereas ”high risk” includes IPSS INT-2 and high risk. This separation is practical since it reflects the different treatment strategies in the two groups.

WPSS

Recently, Malcovati et al published a proposal for an updated scoring system including also WHO classification and the information about a stable transfusion need. This score suggests that patients with unilineage erythroid dysplasia and no stable transfusion need have a prognosis comparable to the average population. Irrespective of the risk group defined by blast percentage and cytogenetic profile, presence of a transfusion need implicated a worse prognosis. This score has yet to be evaluated and is not at present recommended for use outside clinical trials.

WPSS risk group	**Score**	**Median survival Italian cohort (months)**	**Median survival German cohort (months)**
Very low	0	103	141
Low	1	72	66
Intermediate	2	40	48
High	3-4	21	26
Very high	5-6	12	9

Variable	0	1	2	3
WHO category	RA, RARS, isolated 5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	
Transfusion requirement†	No	Regular		

*Good: normal, −Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; and intermediate: other abnormalities.

†At least 1 RBC transfusion every 8 weeks over a period of 4 months.

Additional prognostic factors

- A revised IPSS (R-IPSS, *Greenberg et al*), based on an international, multicenter effort is being launched (not yet published). It is based on 5 (rather than 3) cytogenetic subgroups and results in 5 different prognostic risk groups (very low, low, intermediate, high and very high).

- Also from other groups (*Haase et al*) more refined prognostic risk stratifications based on cytogenetic subgroups have been published.

    - Cytogenetic findings with a good prognosis (median OS > 4 years) includes del(5q), del(20q), -Y, normal karyotype (already defined in IPSS) but also del(12p) and del(5q) + one additional abnormality. Del(11q), +21 and der(1;7) might also be included in this good prognostic subgroup based on some but not other studies.

    - In an intermediate group (median OS 1,5-2 years) are included del(7q), +8, i(17q) and +19 and possibly 11q23 abnormalities.

    - Cytogenetic abnormalities with a poor or very poor prognosis (median OS <1,0-1,5 years) are -7, any 3q abnormality and complex karyotype (≥3 abnormalities)

- Bone marrow fibrosis grade 2 and 3 seems to confer an inferior prognosis

- Point mutations in TP53, EZH2, ETV6, RUNX1 and ASXL1 have been associated with poor prognosis

Recommendation for diagnosis and prognosis

- All patients should be classified according to WHO 2008 classification.
- All patients should be risk stratified according to IPSS.
- Patients who are potential candidates for allo SCT can be risk stratified according to WPSS
- MDS should be reported to the National Cancer registries in all Nordic countries and to MDS specific registries, if applicable.

International Working Group (IWG) modified response criteria

The IWG criteria define 4 aspects of response based on treatment goals: (1) altering the natural history of disease, (2) cytogenetic response, (3) hematological improvement (HI), and (4) quality of life.

Proposed modified IWG response criteria for altering natural history of MDS

Category	Response criteria (response must last at least 4 weeks)
Complete remission	Bone marrow ≤ 5% myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood: Hb ≥ 110 g/l, Platelets ≥ 100 x10^9/L, Neutrophils ≥ 1.0 x10^9/L Blasts 0%.
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5% Cellularity and morphology not relevant
Marrow CR	BM ≤5% myeloblasts and decrease by ≥ 50% over pre-treatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of BM blasts, or progression to a more advanced MDS subtype than pretreatment
Relapse after CR or PR	At least one of the following: Return to pretreatment BM blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hb concentration by ≥ 15 g/L or transfusion dependence
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease progression	≥ 50% increase in blasts Any of the following: At least 50% decrement from maximum remission/ response in granulocytes or platelets Reduction of Hb by ≥ 20g/L Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Proposed modified IWG response criteria for haematological improvement

Hematological improvement	Response criteria (response must last at least 8 weeks)
Erythroid response (pre-treatment<110 g/L)	Hb increase by ≥ 15g/L Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for Hb ≤ 90g/L pre-treatment will count in the RBC transfusion evaluation
Platelet response (pre-treatment<100 x10^9/L)	Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
Neutrophil response (pre-treatment<1.0 x10^9/L)	At least 100% increase and an absolute increase > 0.5 x 10^9/L
Progression or relapse after HI	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hb by ≥ 15g/L Transfusion dependence

Therapeutic intervention and follow up of MDS

We recommend that all newly diagnosed patients are evaluated at a center with hematological experience. Patients should undergo regular follow-up including blood tests. If a patient is considered to be a candidate for therapeutic intervention at disease progression, regular bone marrow analysis is recommended.
Due to the vast heterogeneity of the disease, therapeutic options range from observation only to allogeneic SCT. Decision-making about treatment may be difficult. It is essential that patients are evaluated for curative approaches at diagnosis, since e.g. allo-SCT in progressive phase of MDS has a poor outcome. It is our recommendation that suitable patients are offered treatment within study protocols or, alternatively, are treated according to the recommendations of the Nordic MDS-group.

Algorithm for treatment of symptomatic low-risk MDS

1. High-quality transfusion therapy, and chelation therapy, when indicated.
2. Evaluate patients with IPSS INT-1 for curative treatment (allogeneic stem cell transplantation), in particular in the case of additional risk factors (bone marrow fibrosis, transfusion need, etc).
3. Evaluate patients with RA and RCMD for immunosuppressive treatment.
4. For patients with anemia, consider Epo ± G-CSF to patients with predictive score 0 or 1 according to the predictive model.
5. Patients with severe cytopenia and/or transfusion dependency who have failed other relevant therapies should be considered for experimental treatment within a clinical trial
6. Lenalidomide treatment for IPSS low and INT-1-risk MDS with del(5q) should be used with extreme precaution and not without discussion with a member of NMDS.

Algorithm for treatment of patients with high-risk MDS

1. Evaluate for curative treatment, allogeneic stem cell transplantation.
2. Evaluate patient for azacitidine treatment
3. Evaluate patient for AML like chemotherapy; especially younger patients with good risk features for response.
4. Evaluate patient for low dose chemotherapy.
5. Supportive care only or experimental treatment within a clinical trial.

Algorithm for treatment of patients with CMML

1. Consider allogeneic SCT for both CMML 1 and CMML 2. It is recommended that the patients are in haematological CR, if possible.
2. Patients with CMML 2 (10-29% marrow blasts) and less than 13 x 10^9/L in leukocytes: Azacytidine
3. Patients with CMML 2 (10-29% marrow blasts) and more than 13 x 10^9/L in leukocytes: Hydroxyurea or AML-like chemotherapy may be given.
4. Patients with CMML 1 (5-10% bone marrow blasts) and less than 13 x 10^9/L in leukocytes: Wait and see. Can be treated with Epo according to recommendations for other low risk MDS.
5. Patients with CMML 1 (5-10% bone marrow blasts) and more than 13 x 10^9/L in leukocytes: Hydroxyurea if symptomatic

Supportive Care

Transfusion

A recent study suggests that quality of life is improved with higher targets for transfusion. Use leukocyte-filtered blood products.

Red cell transfusions:

- Transfuse for symptoms of anemia. Planning for transfusion should be made on an individual basis by the patient and the physician, taking into account co-morbid illness as well as quality of life issues. No universal trigger or target for transfusion is recommended.

Platelet transfusion:

- Platelet transfusion is recommended in thrombocytopenic patients with moderate or severe bleeding. A universal trigger value or prophylactic platelet transfusions is not recommended as a rule.

Iron Chelation

Background:
There are currently three different iron chelators available, Desferrioxamin (DFO) to be given by injection or infusion, and Desferasirox and Deferiprone, both given orally, the latter only available in some Nordic countries. With DFO and deferiprone iron is excreted in the urine, rendering the urine red. With deferasirox, iron is excreted entirely in the feces.
Limited data are available regarding the importance of iron chelation in MDS and the recommendations are primarily based on studies in thalassemia. In thalassemia there is strong evidence about the usefulness of iron chelation, and there are reports for all available chelators that they reduce iron overload in MDS. Only for deferasirox a large prospective phase 2 trial has been conducted with 341 patients with MDS being treated for one year. Reduction in median ferritin level and labile plasma iron was observed and the drug was generally well tolerated with gastrointestinal side effects and impairment of renal function most frequently reported. The drug was discontinued in 48.7% of treated patients. For desferrioxamine and deferiprone data are more limited and retrospective in nature.
There are a couple of retrospective studies indicating, that iron chelation may be associated with better overall survival in patients with lower risk MDS. However, there are no studies proving the effect of iron chelation on long-term outcome in MDS. One randomized deferasirox study in MDS is currently recruiting patients worldwide.
No randomized trials comparing the efficiency of the different iron chelators have been conducted in MDS, why no specific recommendations regarding choice of iron chelator can be given.
Practically, oral chelation could be first choice, and if not efficient or tolerable treatment could be changed to desferrioxamine.
The goal of the treatment is to achieve a safe tissue iron concentration by promoting negative iron balance and iron detoxification.

Indication:

- Iron chelation is only recommended in adult patients for whom long term transfusion therapy is likely
- For WHO RA, RARS and 5q- patients iron chelation is indicated, unless very high age, or severe concomitant disease
- In RCMD and more advanced MDS, iron chelation should only be considered for patients with a life expectancy exceeding 2 years from the time point when iron overload has reached the level indicated below
- If iron chelation is indicated, it is recommended to start treatment when S-Ferritin >1500 µg/l, or after approximately 25 units red cell transfusions
- In candidates for allogeneic transplantation iron overload should be avoided. Iron chelation should there be considered to prevent rather than treat iron overload.

Monitoring iron chelation:

- The target Ferritin level is <1000 µg/l.
- In case of rapidly decreasing ferritin to less than 1500µg/l, the dose of iron chelator should be reduced.
- Audiometry and Opthalmology evaluation prior to starting therapy and there after yearly.

Desferrioxamine (DFO)

DFO treatment

- 40 mg/kg (20-50 mg) by subcutaneous infusion over 8-12 hours 5-7 days pr week. Can alternatively be given by slow subcutaneous injection over 30 minutes, dose divided in two.
- Vitamin C 2-3mg/kg/d should be started 4 weeks after the onset of DFO therapy to improve iron excretion.
- Alternatively give DFO 5-10 g via HomePump over 2-5 days from beginning of each transfusion (required that the patient has Port-a-Cath).
- Continuous (uninterrupted) 24 hour DFO should be considered in patients at high risk, e.g. with Ferritin persistently >2500 µg/l and significant cardiac disease.
- In case of severe iron overload with insufficient effect of DFO, it can be combined with deferiprone in usual doses (see below).

Recommendation:
Recommendation grade B, evidence level III.

Oral chelators:

Deferasirox

Treatment

- Deferasirox should not be given to patients with impaired renal function (elevated creatinine)
- 10-40 mg/kg/day once daily – consider slow dose increase with initial dose of 10 mg/kg

- Tablet(s) is dissolved in water or juice. Patient should be fasting, taking the drug at least 30 minutes prior to food intake.
- Liver function tests and creatinine should be measured monthly (creatinine weekly for the first month of therapy).
- In case of elevated creatinine above upper limit of normal, deferasirox should be interrupted, then restarted at lower dose

Monitoring
- Monitoring as with DFO.

Recommendation:
Recommendation grade B, evidence level IIa

Deferiprone

Treatment:
- 75 mg/kg in three divided doses
- Can be combined with DFO to improve the efficiency of iron chelation
- Check blood counts weekly to rule out deferiprone-induced neutropenia, although the reported incidence is probably <1%.
- Not recommended in patients with pre-existing severe neutropenia

Recommendation:
Recommendation grade B, evidence level III.

Tranexamic acid

- For patients with low platelet count and bleeding tendency, tranexamic acid can be considered (1 g three to four times daily)

Recommendation:
Recommendation grade C, evidence level IV.

Treatment and prevention of infections

Infections should be treated promptly and with follow up of outcome. Routine use of prophylactic antibiotic treatment can not be recommended.
The neutropenic patients should be informed to contact the care giver in any case of fever above 38°C for more than 4 hours or any temperature above 38.5°C.

G-CSF treatment: Can be considered as prophylaxis for severely neutropenic patients with recurring, serious infections or during infectious episodes. Published data are limited.

Treatment of low-risk MDS not eligible for curative approaches

Treatment with EPO / Darbepoetin alone or in combination with G-CSF for the anemia of MDS

Background

Treatment with erythropoietin (Epo) may improve hemoglobin levels and alleviate transfusion need in MDS patients with anemia. The effect of Epo may be enhanced by G-CSF, which synergises with Epo to improve survival and proliferation of early erythroblasts. There is one randomised controlled phase III study on Epo alone vs placebo, and one randomised open phase III study on Epo + G-CSF vs supportive care, both showing a significant effect on hemoglobin levels. There are two randomised phase II trials showing better efficacy of the combination compared to Epo alone. In addition, two large retrospective epidemiological studies show a survival benefit for patients treated with EPO±G-CSF compared to untreated patients with no impact on AML transformation. A prospective randomized phase III trial comparing the effect of EPO±G-CSF and placebo on long-term outcome will probably never be performed. In conclusion, there is no doubt about the efficacy of treatment on hemoglobin levels and there are strong indications that treatment is associated with improved survival without impact on transformation rate. Darbepoetin (DA) has been evaluated in some small and one larger phase II trial. The efficacy is comparable to Epo, but not proven superior.

Response criteria for evaluation of erythroid response

For treatment outside clinical trials, we have chosen to use the criteria used in previous publications from NMDSG and in a randomized phase III study published by the French MDS Group. IWG response criteria may, however, be used within clinical trials

Erythroid response

- **Partial erythroid response (PER)**
  - In transfusion-dependant patients: Stable anemia without need for transfusions
  - In patients with stable anemia: Increase of hemoglobin of ≥15 g/l
- **Complete erythroid response (CER)**
  - Stable hemoglobin ≥115 g/l

Decision-making and treatment

Predictive model for treatment of the anemia of MDS with Epo + G-CSF. Extrapolated to DA

Patients should be evaluated according to the predictive model before a decision about treatment.
Hellström-Lindberg E, Br J Hematol. 2003;120:1037-46.
Supported by Jädersten et al, Blood. 2005;106:803-11.

Transfusion need	point	S-Epo	Point
<2 units RBC / month	0	<500 U/l	0
≥2 units RBC / month	1	≥500 U/l	1

Predicted response. 0 point 74%, 1 point 23%, 2 points 7%

Indication for treatment with Epo / DA ±G-CSF in MDS

- Symptomatic anemia

The hemoglobin level required to start treatment must be evaluated individually, and with consideration of co-morbid conditions. Usually no need for treatment if hemoglobin >100 g/l

Positive criteria: (should be established prior to treatment!)

- Verified MDS diagnosis
- Less than 10% blasts
- Score 0 or 1, according to the predictive model. Score 2 patients should not be treated.
- No iron deficiency

Treatment, general aspects

- In general, start with Epo/DA alone for 8 weeks. In case of no response (at least PER), addition of G-CSF for another 8 weeks. RARS patients with regular transfusion need may be treated with the combination from the beginning and for 16 weeks. If no response (at least PER) after 16 weeks, treatment should be terminated.
- If patients on Epo monotherapy loose their response, the Epo dose could be increased or G-CSF can be added. Evaluate after a maximum of 16 weeks.
- Check S-ferritin regularly. If the ferritine value drops below the upper limit of the normal range, start oral or iv iron treatment
- Bone marrow sampling in case of lost response is generally recommended.

Erythropoietin dosing

- **Target hemoglobin level <120 g/l**
- **Induction phase:** The majority of scientific evidence from larger studies on conventional erythropoietin is based on three divided doses / week, but there are several pilot studies using 1-2 weekly doses and the general experience is that this works well. There are no controlled studies comparing different dose regimens.. Start with Epo 30 000 U/week, and increase to 30 000 twice weekly if no response after 8 weeks. Patients with regular transfusion need / higher S-EPO levels may start with 60 000 U/week.
- The starting dose in low weight patients with stable anemia, and always in case of reduced renal function should be lower than 30 000 U/week
- There are a few studies which have reported on the use of Epo doses up to 80 000 U / week, but without comparison with 60 000U/week in divided doses. These higher weekly doses cannot be recommended
- **Maintenance phase**. In case of CER with Hb>120 g/l, decrease the weekly dose every 8 weeks, first increasing intervals between doses, then dose / injection. There are no scientific evidence to recommend any specific pattern of reduction. Median maintenance dose in NMDSG studies is 30 000 U (range 5-60 000), somewhat higher for RARS than RA.
- **Overdose**. If Hb above upper normal range, interrupt Epo treatment and restart at 50% of dose when Hb decreases below approximately 120 g/l. Consider venesectio if supranormal Hb levels

Darbepoetin dosing

- There are no prospective clinical trials comparing different modes of DA dosing in MDS.
- **Target hemoglobin level <120 g/l**
- **Induction phase**. In general, start with 300 µg / 14 days or 150µg /week. Maximum dose in case of no response 300 µg / week.
- A recent NMDSG study showed 2 major thromboembolic events in 30 patients treated with 300µg/week. There are a few additional reports on thromboembolic disease in DA treated

MDS patients. A starting dose of 300 µg/week (suggested to be equal to 60 000 Epo) is therefore not recommended.

- The starting dose in low weight patients with stable anemia, and always in case of reduced renal function should be lower.
- **Maintenance phase.** One study described a median required maintenance dose of 300 µg/week. One study described a median required maintenance dose of 300 µg/14 days. Prolong interval between injections rather than reducing dose / injection
- **Overdose**. See Epo. Darbepoetin may lead to a more dramatic hemoglobin rise than erythropoietin, and considering the longer half-life this may constitute a risk. It may therefore be safer to initiate treatment with conventional erythropoietin in patients with a high probability for response.

G-CSF dosing

- The majority of studies have used G-CSF in 2-3 doses weekly. However, clinical experience suggests that 1-2 weekly doses are as efficient.
- Start with 300 µg (or equivalent) once weekly .
- Treatment should aim at a clear rise in neutrophil count, in previous studies 6-10 x 10^9/l. If no response, increase the dose to a maximum of 300 µg x 3 / week.
- In case of high neutrophil counts, reduce the number of injections / week, then reduce dose / injection (give 50% of amount in syringe).
- Long-acting G-CSF has not been evaluated in MDS and cannot be recommended.

Management of patients in case of a lost response

- There are no published evidence, these guidelines are based on clinical experience
- Bone marrow sample to check for progress + new evaluation according to predictive model
- If no progress and not poor group according to model, individual increase of Epo + G-CSF, if doses are lower than maximal. Do not treat with increased doses for more than 16 weeks.
-

Recommendation Epo
Recommendation grade A, evidence level 1B.

Recommendation Epo + G-CSF
Recommendation grade A, evidence level 1B

Recommendation DA±G-CSF
Recommendation grade B, evidence level IIA

Immunosuppressive treatment

Background

A small fraction of low risk MDS patients with RA and RCMD seem to have bone marrow failure due to autoimmune mechanisms, as known from aplastic anemia. Several international studies have demonstrated response rates in the order of 30% to immunosuppressive therapy (antithymocyte globulin [ATG] in some investigations combined with cyclosporin A [CyA]) in patients with RA and RCMD. HLA-DR15 positivity, young age and short duration of red cell transfusion dependence

seem to predict for a response to immunosuppressive therapy in MDS patients, although this is based on a limited material. A recent analysis of patients treated at NIH indicated an improvement of survival of ATG treated patients, especially in younger individuals with lower risk disease. . A recently published randomized study by Passweg et al. confirmed 29 % response in the ATG/Cyclosporin A arm compared to 9 % in the supportive care arm, but did on the other hand not confirm significant survival improvement.
To date there are no controlled data to support the addition of Cyclosporin A to ATG treatment in MDS, although this combination has been shown to increase the response rate in a recent retrospective analysis.

Decision-making and treatment with ATG

Indications for ATG

- Patients with RA and RCMD with symptomatic and transfusion dependent anemia and/or thrombocytopenia and/or neutropenia with increased susceptibility to infections.

Positive criteria

- Age: <70 years
- IPSS LR or INT-1

We recommend that HLA-DR15 is analyzed in patients who are candidates for immunotherapy. HLA-DR15 positivity will strengthen the indication especially in patients >50 years and with a long duration of transfusion dependency.

Treatment: Follow local guidelines for ATG treatment

- There are different ATG products available, and ATG should be used according to local traditions/experience.

    - horse ATG, Genzyme (Lymphoglobuline™); 15 mg/kg, d 1-5
    - rabbit ATG, Genzyme (Thymoglobuline™); 3.75 mg/kg d. 1-5
    - rabbit ATG, Fresenius (ATG-Fresenius™); 20 mg/kg, d. 1-3
    - horse ATG, Pfizer (ATGAM™); 40 mg/kg, d 1-4 (unavailable in near future)

- Prednisolon: During treatment with ATG, we recommend the addition of prednisolon day 1-24 (1 mg/kg/day d 1-10), then tapering the dose for the following 14 days until complete stop.
- Prophylaxis with sulfamethoxazol/trimetoprim for 6 months is recommended.
- Consider fluconazole and acyclovir prophylaxis

Note
Late response may be observed after treatment with ATG/ CyA. Response evaluation has to wait until 3-9 (3-6) months after start of treatment.

Recommendation ATG
Recommendation grade B, evidence level Ib.

Cyclosporine A treatment

- It is up to the treating physician to decide whether to include CyA, as maintenance treatment in the immunosuppressive treatment. No sufficient published evidence for MDS

- In case of contraindications to ATG, therapy with cyclosporine A alone can be tried. Dosage according to local recommendations (serum CyA around 200 ng/ml is recommended, adjust according to creatinine levels)

Recommendation CyA
Recommendation grade B, evidence level III.

Alemtuzumab treatment

Recent data from a phase 1/2 pilot trial conducted by the NIH group demonstrated the efficiency of alemtuzumab (10 mg iv days 1 to 10) in 77% of 22 evaluable patients with MDS IPSS Int-1 and in 57% of 7 evaluable MDS IPSS Int-2 patients. Although this has not been confirmed by others, the data indicate that alemtuzumab may bean alternative to ATG.

Recommendation Alemtuzumab
Recommendation grade B, evidence level III.

Allogeneic stem cell transplantation (SCT) in MDS

Conventional allogeneic SCT

Background
Allogeneic stem cell transplantation is the only known curative treatment option in patients with MDS and CMML. Register data shows disease free survival rates between 35 and 40%, transplant related mortality (TRM) around 40% and relapse rates 20-30%. Risk factors for TRM are high age, advanced disease stage, therapy related MDS and use of unrelated donor in addition to the presence of comorbidities. Risk factors for relapse are high age, advanced disease stage, poor risk cytogenetics (IPSS). In addition, one study found disease duration to be a risk factor for TRM.

Decision making and treatment
Indications (sibling or unrelated)
- Age below 55-60
- IPSS INT-1, INT-2 and HR. Consideration should be given to additional risk factors (page x)
- Performance status 0, 1 or 2
- No serious co-morbid conditions (pulmonary comorbidities, renal disease, heart diseases etc)

In general, recommendations of the local transplant centre should be followed.

Decision making
- **At diagnosis** consider if the patient is a candidate for allogeneic stem cell transplantation (myeloablative or reduced intensity conditioning (RIC)). It is not recommended to wait for significant disease progression before a decision about allogeneic transplantation is taken.
- In younger patients consider the possibility of underlying rare familial syndromes (Fanconi, telomere-assciated disorders) which may have implications for the choice of conditioning regimen.

- Prior to decision-making regarding allogeneic transplantation, the patient should be thoroughly informed by his/her physician about benefits and risks with transplantation. Any patient must be individually evaluated and should be discussed by the care taking physician and the transplant unit.
- Evaluate patient for potential comorbidities (according to Sorror, Blood 2005, see next page).
- In case of IPSS INT-1, consider immunosuppressive treatment and/or Epo+G-CSF, before proceeding to transplantation.
- In case of decision to transplant – proceed immediately with HLA typing and family work-up. Even potential family donors should be considered as potentially suffering (yet asymptomatic) from the same rare familial disorder as the patient and to be screened for it if suspected.
- If no sibling available, search for unrelated donor.
- All transplant related procedures (conditioning, immunosuppression and supportive care) are performed according to local guidelines.

Cytoreductive chemotherapy prior to myeloablative SCT in patients with high risk MDS (>10% blasts) and MDS/AML

- The value is not established due to lack of randomised trials and conclusive retrospective data. The relapse risk after allo SCT is significantly higher for patients with high blast counts than for patients with CR after induction chemotherapy. On the other hand, induction chemotherapy may in some patients give rise to severe side effects, which prevents SCT.
- Treatment should be determined in close collaboration with the local transplant team and usually involves AML like chemotherapy. If this fails, or if very poor predictive variables;complex karyotype, severe fibrosis, severe infection upfront azacitidine can be considered.

Recommendation conventional myeloablative allogeneic SCT
Recommendation grade B, evidence level IIb.

Reduced intensity conditioning (RIC) SCT

Background

Published series of RIC SCT are still more limited, with smaller number of patients and shorter follow-up. Furthermore, conditioning regimens and immunosuppressive therapy differ considerably. However, when critically evaluated in a systematic evidence-based review it has been concluded that RIC SCT is effective in the treatment of MDS. There are several analyses that have compared RIC transplantation with conventional myeloablative transplantation, and most of them suggest similar outcomes. From the publications, it appears that RIC SCT is feasible and potentially curative even in elderly patients (up to the age of 70 years) with comorbidities precluding ablative SCT. Most studies indicate similar overall survival for individuals undergoing RIC SCT as for those who received myeloablative conditioning. The causes of treatment failure, however, are different with more relapses in RIC SCT patients, but higher TRM in patients receiving myeloablative conditioning. In most series, patients with advanced MDS had remission inducing AML like chemotherapy prior to RIC SCT. Patients, who did not obtain a reduction of blast count to below 5% before SCT, were at high risk for relapse.

Decision making and treatment

Indications (sibling or unrelated)

- Age up to 70 years or below 55-60 with co-morbid conditions preventing conventional conditioning
- IPSS INT-1, INT-2 and HR
- Performance status 0, 1 or 2
- No serious co-morbid conditions that definitely preclude SCT
- In case of advanced MDS, AML like chemotherapy or azacitidine should be given to obtain a reduction of blast count to below 5% pretransplant

Decision making

- See above for conventional SCT.
- Recommendations of the local transplant centre should be followed.

Recommendation

- Recommendation grade B, evidence level IIb

Hematopoietic Cell Transplantation comorbidity index (HCT-CI)

Based on Cox proportional hazard analysis of specific comorbidities in 1055 patients receiving allogeneic SCT at Fred Hutchinson Cancer Center in Seattle (294 RIC and 761 myeloablative), a Comorbidity Index was constructed, which predicts non relapse mortality and survival. It is recommended to evaluate a potential transplantation candidate with HCT-CI prior to referral. The total HCT-CI score is the sum of these integer weights. The HCT-CI scores are divided into 3 risk groups: 0 (low risk), 1 to 2 (intermediate risk), and 3 or more (high risk). The higher the HCT-CI the higher the non relapse mortality (transplantation related mortality) and the lover the overall survival.

Comorbidity	*Definition of comorbidity*	*HCT-CI weighted score*
Arrhytmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease, [§] congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 2 mg/dL (178 mmol/l), on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2
Prior solid tumour	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLco and/or $FEV_1 \leq$ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3

EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide

Treatment of high-risk MDS and MDS/AML in patients not eligible for allogeneic stem cell transplantation

Patients may refuse to undergo transplantation or not be eligible for allogeneic stem cell transplantation due to lack of a compatible donor, comorbidities or advanced age precluding transplantation.

Azacytidine

Background

Azacitidine is approved for treatment of IPSS INT-2 and HR MDS and MDS/AML with 20-30% blasts in patients not eligible for haematopoietic stem cell transplantation.

A randomised phase III study of patients with advanced MDS not primarily eligible for curative treatment (SCT), compared azacitidine to best standard of care (BSC), where the treating physician could choose between best supportive care only, best supportive care with low dose cytarabine or best supportive care with AML-like chemotherapy. The study demonstrated a significant improvement in overall survival with azacitidine (24 vs 15 months, p=0.0001) and time to AML transformation (24 vs 12 months, p=0.004). Twenty-nine % of azacitidine treated patients responded with CR or PR. The benefit of azacytidine compared to BSC has also been proven in sub group analyses of patients >75 years of age, and for AML with 20-30% marrow blasts (former RAEB-t).
Best response was obtained after a median number of 4 courses, underscoring the importance of continuing treatment even if no response can be observed after a few courses.
In the control arm, 25 patients were allocated to AML-like chemotherapy and by subgroup analysis it was shown that these patients also had a shorter survival than the azacitidine treated patients, although this part of the study was not powered for subgroup analysis. Also, the selection of patients to this alternative may have excluded patients with good risk for a response to chemotherapy.
Two recent publications suggest, that azacitidine treatment as a bridging therapy to allogeneic SCT is feasible and does not seem to alter the post-transplant prognosis.

Based on these findings, azacitidine is generally recommended as first choice for HR-MDS and MDS/AML (with 20-30% blasts) unless the patient is young with good prognostic features for response to AML-like chemotherapy. For patients with MDS-AML with more than 30% blasts, evidence based recommendations regarding azacitidine versus AML-like chemotherapy can not be given at present.

Decision making and treatment

Indication

- Mainly indicated in patients who are not candidates for curative treatment, although azacitidine can be also be considered as bridging therapy prior to allogeneic SCT

- MDS IPSS INT-2 and High (in rare instances in INT-1 with severe cytopenias, where all other potential treatment modalities have failed)
- MDS/AML with 20-30% blasts
- Significant cytopenia (if not, follow up frequently)
- Expected survival exceeding 3 months.

Treatment Azacitidine

- Azacitidine 75 mg/m^2 sc d 1-7 repeated every 28 days. (alternative dosing schedules can be used if requested by patients eg 100 mg/m^2 sc d 1-5).
- Continue treatment unless obvious signs of progression. Obvious signs of improvement are rarely observed after only 1 to 2 courses of treatment.
- Evaluate response (bone marrow assessment) after 4-6 courses unless there is overt progression or indications of overdosing earlier. Allow sufficient time (5-6 weeks) after last course before marrow evaluation, to avoid azacitidine induced hypoplasia/marrow suppression at time of evaluation.
- In case of response, recovery of peripheral blood values may be delayed due to suppressive effects of azacytidine. It may be useful to make an 8 weeks pause after cycle 6 to see if recovery occurs.
- It is not totally clear how to proceed in case of a complete or partial remission after 6-8 cycles. The MDS 001 trial and the European label recommend continuous treatment with unchanged dose. However, many patients will not tolerate this treatment, and in elderly/fragile patients it may be a good choice to stop treatment and continue in case of progression. Another option is decrease the dose / cycle and /or increase dose intervals to 5 weeks. It is at the moment difficult to make specific recommendations and we recommend discussion with regional/national coordinators.
- Specific guidelines including instructions to nurses may be obtained from the Nordic MDS group coordinators.

Recommendation

Recommendation grade A, evidence level 1b.

AML like chemotherapy

Background

A number of studies have been published where a total of more than 1100 patients with HR-MDS or MDS-AML have been treated with different combinations of induction chemotherapy. Only few studies were randomized, and then often with the purpose to study the effect of G-CSF or GM-CSF in combination with chemotherapy. All studies taken together showed a median complete remission (CR) rate of 43% (range: 18-74%), and overall survival (OS) varying between 6-21 months. Between 8-27% of the patients died within the first month of treatment. Patients with normal LDH and/or WBC <4x10^9/l and absence of poor risk cytogenetics had better CR rates. In some studies, duration of antecedent MDS was inversely related to achievement of CR. CR durations are generally short and there is no evidence, that AML like chemotherapy alters the natural history of

MDS, ie overall survival is not affected by the treatment. There are no data to support that high dose chemotherapy with autologous stem cell support is superior to AML like chemotherapy. Hence, no recommendation can be made as to the preferred use of autologous stem cell transplantation in younger HR-MDS and MDS-AML patients.

Decision making and treatment

Indication for AML like chemotherapy
Consider younger patients with high-risk MDS (IPSS INT-2 or HR) and MDS-AML

- Remission induction of younger patients prior to allogeneic SCT
- In patients not eligible for allogeneic SCT if
    - good prognostic features for CR, ie normal s-LDH and/or WBC <4.0 x10^9/L, good or intermediate risk cytogenetics
    - deemed to tolerate induction chemotherapy.

In elderly patients with high-risk MDS (IPSS INT-2 or HR) and MDS-AML (less than 30% blasts),

- azacitidine is recommended as first choice.
- in elderly, where azacitidine has failed, AML like chemotherapy can be attempted in patients in good performance status, without comorbidities and with good prognostic features for achievement of CR

Choice of induction therapy
Based on efficacy and toxicity data, it is recommended that:

- Patients are treated with standard AML induction chemotherapy according to local protocols.
- In cases where CR is not reached after one induction course, a second identical induction course is indicated, provided the first one significantly reduced the bone marrow blast cell count and was not too toxic.
- NB: it is not uncommon that a CR is reached late, 6-10 weeks after induction chemotherapy. This probably reflects the reduced number of remaining 'normal' stem cells present in MDS.

Recommendation AML like chemotherapy:

- Recommendation grade B, evidence level IIa

Low dose chemotherapy

General background

There is insufficient evidence to recommend routine use of low-dose chemotherapy, since there are no data showing a beneficial effect on survival or transformation to AML in unselected groups of

patients. However, in individual patients low-dose chemotherapy may be used to reduce high white blood cell counts as well as bone-marrow blast counts, and to improve pancytopenia in MDS.

Melphalan

Three small phase 2 studies in high-risk MDS patients report a response rate of up to 30 % in selected patients, i.e improved blood cell counts and reduced/abolished transfusion need. The toxicity was mild.

- Suggested indication: Symptomatic high risk MDS and MDS/AML patients with a normal karyotype and a hypo/normocellular bone marrow.
- Dosage: 2 mg/day until response (usually 8 weeks) or progression.

Recommendation grade B, evidence level IIb.

Low-dose cytosine arabinoside

One large randomised study comparing low dose cytosine arabinoside (LDAC) and supportive care in predominantly high-risk MDS patients showed a response rate of approximately 30% in the LDAC arm, but no benefit in terms of overall survival and transformation to AML. Fatal hematological toxicity at a frequency of up to 19% was reported for LDAC. Ara-C has in a subgroup analysis of the Aza 001 trial been shown to be inferior to azacytidine (include that ref in refl list)

- Suggested indication: Symptomatic cytopenia in individual cases of high-risk MDS. A predictive model for the clinical response to LDAC suggests that a low platelet number and chromosomal aberrations at diagnosis indicate a low response rate.
- Dosage: Ara-C 10-30 mg/m^2/day sc, for 2-8 weeks. Maintenance treatment might be given to responders.

Recommendation grade A, evidence level Ib

Chronic myelomonocytic leukaemia

Background

Chronic myelomonocytic leukaemia is a rare disease with an incidence of 3/100.000/year in a population > 60 years, M:F ratio is 2:1, median age at presentation is 65-75 years. 15-20% transforms to AML. The disease has both myeloproliferative and myelodysplastic features. In 1994, the FAB group proposed to separate CMML in a proliferative form with white cell counts >13 x 10^9/L, and a dysplastic form with white cell counts below 13 x 10^9 /L. It is unclear if there is a prognostic difference between the proliferative and the myelodysplastic variant, some groups have seen a worse prognosis in the proliferative arm (Onida), others have not seen this (WHO)

Diagnostic criteria (according to WHO):

1. A persistent monocytosis of >1 10^9 per liter with a percentage of monocytes >10% of WBC, not due to other causes. Follow-up after 3 months can be advised to exclude other causes of monocytosis
2. BCR-ABL negative.
3. No rearrangement of the PDGFRA or PDGFRB genes.
4. No more than 20% blasts, and this includes myeloblasts, monocytes and promonocytes
5. Dysplasia in one or more lineages.

Clonal abnormalities can be found in 20-40% of cases, but none is specific for CMML. TET2 mutations have been reported in 46% of the CMML cases, but with no certain effect on the prognosis. JAK2 mutations can be seen, especially in the proliferative variant

The WHO 2008 classification divides CMML into two groups based on the number of blasts: CMML 1: < 10% medullary blasts and <5% peripheral blasts, CMML 2 : 10-19% blasts and /or 5-19% peripheral blasts, with a median survival of 18 vs. 12 months for CMML 1 and 2, respectively.

Different scoring systems have been proposed. IPSS does not include CMML with white cell counts >12 x 10^9 /L. Kantarjian et al have suggested a new IPSS model that also includes secondary MDS and CMML with a high white cell count. Poor prognoostic factors were poor performance, older age, thrombocytopenia, anemia, increased bone marrow blasts, leukocytosis, chromosome 7 or complex (>or=3) abnormalities, and prior transfusions.

Decision-making and treatment

At diagnosis, consider if the patient is a candidate for allogeneic stem cell transplantation (younger patients with negative prognostic features for survival as described above).

Patients with only monocytosis and no symptoms can be followed without treatment.

Indications for treatment are: Fever, weight loss/wasting, cytopenia, symptomatic splenomegaly and disease progression with increasing blast counts. Other leukemic manifestations, such as gingival hyperplasia, leukemic infiltrates in the skin, low-grade DIC or serious DIC-fibrinolysis, may also be indications for treatment.

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation remains the only option for cure in CMML, but still, the TRM is relatively high (25-41%). Allogenous SCT with reduced intensity does not have a higher relapse rate than full conditioning regimen, and the TRM rate was not higher for CMML than for other types of MDS (observation based on limited number of patients). In a retrospective EBMT study of CMML patients only, patients transplanted in CR had a significantly lower probability for non-relapse death (p= 0,006), implying that it is important to treat patients to CR before going to transplantation.

Recommendation allogeneic SCT and RIC
IIa, level B

See the general discussion on allogeneic SCT page 22.

Hydroxyurea

One randomized trial with Hydroxyurea (HU) vs. VP 16 showed superiority in response (60% vs.36%). survival in the HU arm were 20 months vs. 9 months in the VP 16 arm. The responses were, however, short.
Hydroxyurea is recommended as first-line treatment for elderly patients with a low (<10%) marrow blast count and for which the main aim is to reduce symptoms and not to prolong survival. For these patients side effects of HU are clearly milder than for azacytidine
In case of no response to HU or signs of progression of the disease, consider azacytidine as second-line treatment (see below).

Recommendation:

Recommendation level IIa, grade B

Azacytidine

Background

Both FDA and EMEA have approved 5- azacytidine for treatment of IPSS INT-2 and HR MDS and MDS/AML with 20-30% blasts in patients not eligible for haematopoietic stem cell transplantation and CMML with 10-29% marrow blasts without a myeloproliferative disorder (leukocytes less than 13x 10^9/l).
One retrospective single center study has looked at the effect of azacytidine in both CMML with a white cell count more and less than 13x 10^9/L, with an OR in 39% of the cases, with a better response in the MDS-CMML-group compared to the MPD-CMML-group; the differences were not significant
There are few studies specifically designed for CMML, but there are reviews that have analyzed the CMML cohort within larger studies. Generally, but based on small patient numbers, CMML responds well to both 5-azacytidine and decitabine. For CMML with less than 13x 10^9/L leukocytes, with an increase of blasts and for which there is an aim to prolong survival, 5-azacytidine is recommended as1st line treatment. Treatment should be planned to given for at least 6 cycles.

Recommendation:
Recommendation grade A, evidence level 1b.

Treatment alternatives which are not commercially available or of uncertain usefulness

We here report on a selected number of potential therapeutic candidates which are in clinical trials but not commercially available. We have also chosen to include information about drugs that we do not recommend, but that we know sometimes are used in MDS.
We do not give detailed treatment instructions for non-licenced drugs – these can be obtained as guidelines given on the closed part of the NMDS website.

Steroids

Both prednisolone and anabolic steroids have been tried for MDS. Most reports are relatively old and very small, and there is no evidence of a significant response in terms of improved cytopenia. Generally, steroids should be avoided due to their side effects.
According to clinical experience, MDS with a significant inflammatory component, as mirrored by high sedimentation rate, arthritis, and other inflammatory symptoms, may occasionally respond in terms of improved general symptoms to moderate doses of prednisolone.
Recommendation: Generally not recommended
Anecdotal non-validated reports have also shown that the thrombocytopenia of MDS occasionally may show a temporary response to anabolic steroids
Recommendation: no general recommendation

Decitabine

Background
DNA hypermethylation is common in high-risk MDS and AML and seems to predict for progression of the disease. Azacytidine and Decitabine are chemotherapeutic agents that, in low doses, may cause demethylation of genes and re-expression of i.e. cell cycle control proteins.

A large phase II study showed that Decitabine had significant effects also in high-risk MDS, and that major cytogenetic responses could be observed in 19/61 of responding high-risk MDS patients, even in the IPSS high risk cytogenetic group. This has been confirmed in a recent randomized trial of decitabine vs best supportive care, which showed a trend towards longer median time to AML progression or death, although no significant survival advantage of decitabine treatment could be demonstrated. Higher complete response rates (using the less demanding modified IWG response criteria) ranging from 21 to 39% using three different dose schedules of decitabine were obtained in a recent randomized single centre trial.
With decitabine, best response was obtained after a median number of 3 courses, underscoring the importance of continuing hypomethylating treatment even if no response can be observed after a few courses.
Recently, an EORTC study comparing low-dose decitabine to best supportive care in 233 higher risk MDS patients age 60 years or older and ineligible for intensive chemotherapy showed, that decitabine treatment resulted in improvements of OS and AML-FS (nonsignificant), of PFS and

AML transformation (significant) and of patient-reported QoL parameters. Lübbert et al. JCO 29, April 11, 2011

Status
Decitabine is approved by FDA and commercially available in the US (Dacogen©). Decitabine is not commercially available in most countries in Europe and the decision from EMEA is pending.
Indication
- MDS patients with significant cytopenia
- IPSS INT-2 and High (in rare instances in INT-1 with severe cytopenias, where all other possible treatment modalities have failed)
- Not candidates for curative treatment or induction chemotherapy

Treatment Decitabine

- Decitabine 15 mg/m^2 by iv infusion over 3 hours every 8 hours, d 1-3 repeated every 6 weeks.
- Evaluate response (bone marrow assessment) after 4 courses unless there is overt progression earlier
- Continue treatment until progression, even in the absence of haematological improvement.

Recommendation
Decitabine: Cannot be made until approval within EU

Thalidomide

Background
Thalidomide is a drug with multiple and not fully understood mechanisms of action. Its potential effect in MDS has been proposed to be through TNF alpha inhibition and anti-angiogenetic effects. One randomized study in AML/ high risk MDS showed no clinical benefit. Raza et al showed 29% (15/51 evaluable pt) erythroid response in low-risk MDS, with 10 patients becoming transfusion independent. No complete responses were observed. These response rates have been confirmed by other studies, and also Epo-resistant patients may respond. However, all studies show very high toxicity with 30-35% discontinuation due to severe side effects (also responding patients). Concerns also about the use of thalidomide in high risk MDS (reports of rapid progression to AML on Thalidomide therapy).

Status
Not approved for MDS. Larger studies ongoing.

Indication
No general indication in MDS. Responding patients seem to be of RA subtype.

Recommendation
Thalidomide cannot be generally recommended, and should definitely not be given to elderly patients. Thalidomide is teratogenic and should not be used in fertile women with MDS

Lenalidomide

Background

Lenalidomid is an immunomodulatory drug (IMiD) licensed for treatment of multiple myeloma. One small and one large phase II study have shown high response rates in epo-refractory low and INT-1 risk MDS patients with a 5q deletion. Transfusion independency was achieved in 67% with a median duration of response of 116 weeks and a cytogenetic response rate of 73%. In this study severe (grade III-IV) neutropenia and thrombocytopenia occurred in approximately 50% of the patients. A recent large randomized phase II trial (placebo vs two doses of lenalidomide) with cross-over at 16 weeks confirmed an erythroid response rate of 56% in patients treated with 10 mg/day 21/28 days, and 43% in patients treated with 5 mg daily. Median duration of response was approximately 2 years. Cytogenetic response rates were 42.5% (10 mg group) and 21.6% (5 mg group). Overall survival in the study was 35-42 months. For the lenalidomide groups combined, 3-year overall survival and risk of AML were 56.5% and 25.1%, respectively. At 5 years, approximately 40% of patients have progressed to AML, with similar frequencies in patients with and without a cytogenetic response to treatment. Whether the risk for progression to AML is higher in treated than in untreated patients is still a matter of investigation, but it is clear that a substantial proportion of patients progress to AML and that younger potentially curable patients should be subject to evaluation for curative regimens.

With improved understanding of disease biology, targeted therapies offer the prospect of greater precision. A recent study demonstrated small subclones with TP53 mutations in 18% of patients with low and INT-1-risk del(5q) MDS, with significantly poorer outcome in patients carrying mutations. In high-risk MDS and AML patients with del(5q), mutations were associated with lower probability of response to lenalidomide.

CHMP Statement 23/09/11 Lenalidomide regarding risk for secondary primary malignancies (SMP) <u>in myeloma</u>

The CHMP concluded that an increased risk of new cancers, such as skin cancers and some invasive solid tumours, was observed in studies in the approved population. There were 3.98 cases of new cancer for every 100 patient-years in patients receiving Revlimid compared with 1.38 cases in those not receiving Revlimid (patient-years is the sum of the lengths of time all patients have been under treatment). The risk for SMP in clinical trials of newly diagnosed myeloma has been reported to 7% compared to 1,8% in controls.

The CHMP weighed the benefits of Revlimid against the risks in the approved patient population (patients who have already been treated in the past). It concluded that its benefits, such as improved survival, continue to outweigh its risk but recommended that the prescribing information for Revlimid be updated with a warning and advice to doctors on the risk of new cancers. The prescribing information will also be updated with data in newly diagnosed multiple myeloma showing a four-fold increase in the number of new cancers in patients being treated with Revlimid.

Doctors are also reminded that the current review concludes that the benefits of Revlimid outweigh its risks in the approved population (second-line myeloma treatment and in combination with dexametason). The CHMP's conclusion does not cover its use in patients for whom the medicine has not been approved. Celgene has in October 2011 written a letter stating that use of lenalidomide outside the approved indication should *only* be performed within clinical trials.

Status for MDS with del(5q)
Lenalidomide is approved by the FDA for the treatment of transfusion dependent low and int-1 risk MDS associated with a 5q deletion with or without additional cytogenetic abnormalities in 2005. EMEA did not approve lenalidomide in MDS, final decision may 2008 EMEA/CHMP 271288/2008. The main reason is an uncertainty whether the drug may enhance the rate of leukemic transformation or not.

Management of treatment with lenalidomide in patients with low and INT-1 risk MDS with del(5q)

- Never treat a patient who may be a candidate for allogeneic transplantation
- Considering the decision of EMEA, patients with low and INT-1 risk MDS and a karyotype involving del5q should preferably be treated within clinical trials, however at the moment few such alternatives exists within the Nordic countries
- In the absence of a clinical trial, severely transfusion-dependent patients with low and INT-1 risk MDS and a karyotype involving del5q could be candidates for treatment. NMDSG strongly recommends that all these patients are discussed with a member of NMDS prior to treatment and that patients are reported to the NMDSG registry, www.nordicmds.org.
- Prior to lenalidomide treatment, patients should be thoroughly informed about the increased risk of other malignancies, which has been observed in multiple myeloma patients.
- Patients with high-risk myeloid disease (including MDS INT-2 and High-risk) with a karyotype involving del5q, or non del5q low and INT-1 risk MDS should only be treated with lenalidomide within clinical trials. No compassionate use is indicated.

Clofarabine

Clofarabine is a purine nucleoside analog that works primarily via inhibition of DNA biosynthesis and the ribonucleotide reductase enzyme with recent evidence suggesting that at low doses it may affect DNA methylation. Clofarabine has shown activity in patients with high risk MDS. Clofarabine is currently available in an intravenous form with an oral formulation presently under investigation. No optimal dose schedule and route of administration has been identified in MDS.

List of other therapeutic options currently in clinical trials

Histone deacetylase inhibitors. Ongoing.
Clofarabine. Ongoing
Inhibitors of angiogenesis. Ongoing
Combination therapy involving TPO agonist

Ongoing MDS trials within the Nordic Region (including trials of the Nordic MDS Group)

See www.nmds.org

Disclosure statement

EHL: advisory board Celgene, research grant for clinical trials Celgene. Unrestricted educational grant from Amgen, Novartis and Celgene. Invited speaker for Novartis and Celgene
LK: Consultancy for Novartis
LN: Honorarium for lectures from Celgene
HG:None
ID: None
MH: None
AL: None
FL: None

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